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## STUDIES OF THE ENDOCRINE GLANDS

### V. The Adrenals

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In a series of previous papers the authors have described an objective method for the diagnosis of endocrine disorders (1) and the results obtained from its application to several of the recognized members of the endocrine group (2). The present paper presents the results which have been obtained with the few adrenal cases which we have been privileged to see. Contrary to the relative frequency with which pituitary, thyroid, and ovarian disorders are encountered, demonstrable adrenal disease seems to be of very rare occurrence. Osler (3) saw only seventeen cases of Addison's disease in the course of twenty-one years. Boothby and Sandiford record but thirteen Addisonians in a series of two thousand four hundred and seventeen (2417) cases studied at the Mayo Clinic. As they report over six thousand thyroid cases in a parallel series, the relative infrequency is strikingly illustrated, particularly as these two groups are drawn from material many times as extensive. In other words, cases presenting the classic signs of adrenal disease as described by Addison, are most infrequently encountered. That the syndrome is implicit in disturbed function of the adrenal glands is generally accepted, although Lewin's (5) collected series of five hundred and sixty-one cases included 12 per cent without demonstrable lesion, a finding frequently recorded by other and later observers. Further, opinion is by no means unified today as to the relative importance of the cortical and medullary portions in determining the disease picture. In spite of these and other seemingly contradictory observations, the intrinsic association of lowered adrenal activity with the Addisonian syndrome may be regarded as definitely established. A similar authority does not obtain for that other type of adrenal failure which is assumed to result from a lowered functional activity and to be unassociated with gross anatomical changes in the gland. This syndrome, possessing many of the characteristics of Addison's dis-

case such as asthenia, hypotension, and usually emaciation, has been in large measure developed by the work of the French clinicians, [See among others, Sergeant (6) and Lucian and Parisot (7)], while in this country, Sajous (8) has been the earliest and major contributor in defining this condition. Incidentally, it should be said that this syndrome more nearly equates with the picture of adrenal insufficiency as produced in numberless animal experiments involving interference but not complete extirpation. A complete Addisonian has yet to be produced experimentally. A third type of failure, chiefly associated with suprarenal hemorrhage, is an acute condition usually terminating fatally in a few days. In addition, a variety of intermediate states have been described but they lack clarity of outline, and in many instances depend upon a mass of wholly unproven assumptions for their very existence. Of the many so-called pluriglandular syndromes, in largest measure also the work of the French school although clinicians of all nations have synthesized diverting combinations of impressive intricacy, but little notice need be taken. The endocrine glands severally and individually are among the potent regulators of general metabolism. In the impairment of one, as in a similar condition with any of the equally important non-endocrine factors, havoc is wrought in many of the delicately balanced equilibria associated with normal function. In the disturbances thus engendered, it is inevitable that other endocrine as well as non-endocrine foci will participate, and in their several dysfunctions influence the terminal disease picture. But their participation is secondary and resultant, not primary and causative. To illustrate, the amenorrhoeas of thyroid and pituitary failure need not derive from the primary failure of the endocrine activity of the ovary any more than when the condition arises in non-endocrine disease wholly unassociated with the generative system. The use of ovarian extract to combat this condition is as illogical as it is ineffective.

In the preceeding paper in this series we analyzed the 22 pluriglandular cases which have come under observation in the course of examination of nearly four thousand patients. It is enough to say here that with but minor exception the pluriglandular element derives from the superposition of surgical ablation of one gland upon the functional disturbance in another. In a single case, unique in our experience, we observed both a surgical dysthyroid state and partial castration added to a probable pituitary dysfunction, which was seemingly the original endocrinopathy.

Reverting to the immediate thesis, we find a well established entity in Addison's disease and one equally demonstrable in the acute and rapidly fatal condition, deriving from hemorrhage in the gland. Of the third for which, of the many presenting, we will select the term "hypo-adrenalism," there is a less certain foundation of proven and tested fact, yet enough authoritative observations exist to render consideration necessary.

Frank under-function would seem to connote the existence of an antithetical picture in which a complementary over-activity of the gland is manifest. In the earlier paper on the gonads (2) we have recorded our

failure to observe such a condition in our cases involving the primary sex organs. With the adrenal, however, several well marked and rather striking anomalies are frequently associated with alleged hyperactivity of the gland, and brief analysis of these is germane to the text.

Precocious puberty is frequently associated with tumors of the adrenal cortex, and the assumption made that hypernephromata condition on over-activity of the gland. Unfortunately for clarity of definition, the same series of somatic and functional changes have been associated severally with the thymus, pineal, the gonads themselves, and less dubiously, the anterior lobe of the pituitary.\* The lack of etiological specificity here greatly enhances the difficulty of the diagnostic problem. Tumor development in adult years is believed to result in an inversion of sex characteristics to which the term "virilism" is usually applied. Cases are also recorded in the pre-adolescent period. The condition is largely confined to the female sex and is intrinsically a masculinization of the secondary sex characteristics. It should not be confused with precocious puberty which is, as the name implies, an abnormally early maturation along wholly normal lines. Virilism connotes an inhibition of the exocrine manifestations of the sex involved. Modification in the differential sex distribution of body hair (hirsutism) is but one item in the general picture of virilism. It may occur alone, however, or at least without well marked evidence of the other features of a true virilism. It has frequently been recorded in connection with ovarian changes, and it is interesting to note that in the eight cases cited by Falta (9) to associate hirsutism with tumor of the suprarenal, five patients had coincident pathologic changes of the ovary, one "small" ovaries, and in the case of the other two no statement is made concerning the gonads.

Another genital anomaly presenting diverse manifestations is pseudohermaphroditism. True hermaphroditism has never been certainly observed in man. Burden (10) records a case with independent ovaries and testes on each side and Neugebauer (11) cites only five established cases of a single ovotestis. Neumann (12) has recorded some later cases in which there may be a larger measure of support for the thesis but he is skeptical of the accuracy of the conclusions drawn by the authors in many of the cases which he cites. Falta seemingly regards the condition as possibly arising from aberrant adrenal function, a position which has apparently been rather generally adopted [Glynn (13)]. To support his thesis, Falta cites the fact that Neugebauer, in his comprehensive work on the subject, records thirteen cases showing disorder of the adrenals. Inasmuch as Neugebauer records over twelve hundred observations, and further, as in this series he reports sixteen cases each showing neoplasm of ovary or testis, the warrant for so sweeping a generalization would seem to be lacking. Further, several of Falta's quoted supporting cases showed simultaneous involvement of the gonads. The rare conditions

\*The literature is fairly extensive, and excellent summaries are to be found in several texts, which emphasize the clinical aspects of endocrine disorders.

designated as "progeria" [Gilford (14)] and "nanism type senile" [Variot and Pironneau (15)] would seem to have but tenuous claim to a purely suprarenal etiology. To summarize then, while the adrenals apparently exercise some influence over the genital sphere, it is far from well defined and is very far from being a unique attribute of this member of the endocrine group. Further, the a priori assumption that cortical tumors determine an over-activity, but ill equates with the observations of neoplasms of the thyroid or pituitary. Lastly, those pictures which may with most certainty be correlated with adrenal disease fail signally to present a uniform antithesis to that offered by the established failure producing Addison's disease.

As the adrenal is essentially two glands, there should be several dysfunctional possibilities, and conceivably certain of the conditions already touched upon could fall in this category. Unfortunately our knowledge of adrenal disease in man is very limited, and the essential nature of its function precludes those surgical interventions that have done so much to clarify our knowledge of certain of the other endocrines. There is, of course, a vast number of most interesting and informative data in relation to animal experiments. As the vast majority of these were designed to throw light on certain physiological problems, data that are applicable to clinical conditions are in the nature of by-products. Further, as we have emphasized in earlier writings, the metabolic divergences of the several species make difficult if not impossible an equation with man. Finally, the results of acute experiments cannot be translated into terms of the chronicity of human disease. Happily, Addison's disease is a rock in the troubled sea of conjecture, surmise, and assumption, and its study offers a sure line of approach to the better comprehension of one phase of disturbed adrenal function. The carefully recorded clinical and laboratory studies of this condition are of the greatest value.

Turning to our own brief series, we must acknowledge initially some difficulty in classifying all of the composing members. Accepted opinion warrants the designation of the Addisonians as hypofunctional cases (I). Far less clear cut are the indices of functional level in the few other cases

TABLE I.  
CLASSIFICATION OF CASES

I	Addison's Disease.....	3
II	Hypo-adrenalism, probable.....	6
	Hypo-adrenalism, possible .....	3
III	Pubertas Praecox.....	1
Total.....		13

(II) that we record. In one or two even, doubt exists as to the warrant of inclusion with the seemingly established adrenal cases. As they conform, however, to the criteria established, and as further, they have shown inter-

esting response to the exhibition of adrenal medication (to be discussed later), we feel that they may be included with a frank statement of their dubious character. A single case of "pubertas praecox," seemingly deriving from an adrenal condition, constitutes a third group (III). For the sake of clarity, the composition of the series may be tabulated and in the subsequent summaries the data from each group will be collated separately.

We have had contact with two other cases of Addison's disease (one of them without pigmentation but with diagnosis verified at autopsy). As they were not completely studied, they are omitted from the series. Such measurements as were obtained, however, are in strict accord with those of the cases reported.

TABLE II  
PHYSICAL MEASUREMENTS

Observation			I	II	III
Sex	Male		1	3	0
	Female		2	6	1
Age	High	(yrs)	61	62	
	Low	(yrs)	32	22	
	Average	(yrs)	47	38	7½
Height	High	(cm)	177	175	
	Low	(cm)	158	154 5	
	Average	(cm)	166	165	115
Sitting Height	High	(cm)	92	96	
	Low	(cm)	85	84	
	Average	(cm)	87	88	64
Sitting Height	Index	Average	0 524	0 533	0 557
Chest	High	(cm)	80	107	
	Low	(cm)	69 5	61	
	Average	(cm)	73 5	75	56
Weight	High	(kgm)	61 4	89 0	
	Low	(kgm)	48 0	34 8	
	Average	(kgm)	53 2	56 0	22 0
Area	Average	(sq m)	1 57	1 60	0 82
Lung Volume	High	(cc)	2200	4100	
	Low	(cc)	1820	2100	
	Average	(cc)	2040	3060	1700

Following the practice of the earlier papers, the physical measurements and certain other statistics are presented in Table II. If the values tabulated here be compared with those summaries given in the first endocrine paper (1), it will be noted that certain discrepancies appear. These derive from the fact that the two groups are not identical in composition, several doubtful or incomplete cases in the earlier series having been replaced by later and more definite cases or by subsequent completed studies on untreated cases whose earlier records were not complete. The trends exhibited by the first series are more definitely established by the present group.

Fortuitously, the sex ratio in Groups I and II is the same, rendering the average values comparable. The average age of the Addison group is higher and the disease condition more severe (all of the patients have



died during the past year) than with those having functional failures of whom but one or two were probable incipient Addisonians. These differences are reflected in the several figures given above. The predominance of the females is certainly fortuitous, as the existing statistics indicate the reverse or, at most, a relative parity of incidence. We wish at this time to emphasize our consciousness of the limited number of data in this series, and the complete lack of warrant for any broad generalization. Only the paucity of similar reports in the literature and the necessity of considering adrenal conditions as an integral part of any general method dealing with the endocrine glands leads us to present this compilation. The rarity of the condition—less than one-half per cent in our series of cases originally selected on the basis of probable endocrinopathy—means the lapse of a considerable time before an adequate number of observations could be available. As acutely conscious as the reader, of the limitations of this

TABLE III  
"VITAL CAPACITY" COMPARISONS

Observation	I	II	III
Weight.....High.....(kgm.)	+10	+17	
Low.....(kgm.)	-31	-36	
% above normal....	33	22	
Average.....(kgm.)	+10	+15	
% below normal....	67	78	
Average.....(kgm.)	-21	-15	
*Total avg....(kgm.)	-11	-8	-3
Chest.....High.....(cm.)	-4	+15	
Low.....(cm.)	-10	-17	
% above normal....	0	33	
Average.....(cm.)	—	+8	
% below normal....	100	67	
Average.....(cm.)	-7	-13	
*Total avg....(cm.)	-7	-5	-2
Lung Volume....High.....(cc.)	-29	± 0	
Low.....(cc.)	-51	-29	
% above normal....	0	0	
Average.....(cc.)	—	—	
% below normal....	100	100	
Average.....(cc.)	-47	-14	
*Total avg....(cc.)	-47	-14	—

\*Weighted for number of cases.

report, we offer it as a first approximation and as indicating tendencies only and not defining limits. The ages are similar to those of the other endocrine groups. The one child (III), a girl of seven, will be discussed later in the body of the paper. The heights are in no way remarkable nor indeed are the other values determined by the bony structure. The Sitting Height-Chest Ratio exceeds that which would be determined if only women were considered, and indicates probably that degree of emaciation which subsequent comparisons disclose. Taking Dreyer's (16) figures as the best available, the normal male ratio would be 1.053, the female 1.152 or, weighting for relative representation, the normal value would be 1.119. Group I gives the value 1.184, and Group II the slightly lower value of 1.173. The weight averages are below those recorded in the other endocrine groups. The average lung capacities of Groups I and II reflect

the degree of asthenia incident to the progress of the disease. Interestingly, that for Group II compares favorably with the group averages of the other endocrine series.

As previously noted, the absolute data frequently are less informative than comparisons with so-called normal standards. Following our earlier practice these may next be considered.

Applying the comparisons with the Dreyer and West standards, as described in the earlier papers, it is obvious that while a few of the cases were overweight, the majority fell below prediction and the net average was actually 11 per cent for Group I and 8 per cent for Group II below that calculated. In passing it may be said that in our entire series of studies this gland is the only one determining a negative average. The

TABLE IV  
URINE DATA

Observation	I	II	III
Volume .... Average... (cc)	750	1240	480
Specific Gravity..Average .	1 011	1 016	1.007
Albumin ... Positive . (%)	100	100	100
Casts .... Positive. (%)	67	44	0
Sugar..... Positive. (%)	67	33	0
Urobilinogen.. Positive. (%)	0	0	0
Salol... . Average.. (min)	70	79	75
Urea Curve.. Normal.. (%)	33	*14	—
Low.... (%)	67	*86	—
Phenol-Sulphone-Phthalein, 2-hour elimination.... Average..... (%)	53	47	53

\*Test not applied to two cases

loss in predicted lung volume is of very significant magnitude in Group I but, oddly enough considering the asthenia characteristic of these cases, in Group II is somewhat less in amount than that observed with the other endocrine glands. The elimination, in this group, of obesity, an other depressing factor of predicted lung volume, may explain the observation.

Certain of the observations, where the urine was the material examined, are collected in the next table.

The individual volume and specific gravity values show fluctuations analogous to those of the other series; the average of Group I shows a lowered kidney permeability while that of Group II equates well with normal findings. The incidence of an albuminuria in 100 per cent of the cases, with casts in significant amount in one-half, offers a significant datum. Further, the presence of glycosuria in over 40 per cent of the cases raises a question that will be considered in detail under the caption of "carbohydrate tolerance." From the standpoint of differential diagnosis, the absence of "urobilinogen" is noted. Others have noted both increases and decreases in normal urine pigment, and Mc Mann (17) has recorded a

single instance of the presence of a foreign pigment. The 'phthalein test would seem to indicate a somewhat lowered kidney permeability, but the extraneous factors influencing this test limit its authority. The provocative urea curve, on the other hand, is most suggestive and corresponds well with the other evidences of kidney disease. In comparison with the groups of the other endocrinopathies and with a large non-endocrine group (some fourteen hundred cases in all), we find that a low curve of elimination is shown in about 20 per cent as contrasted with the 80 per cent here observed. The Salol index is a high average value indicating in the present instance rather the lowered renal permeability than an impaired gastric motility. The partition analysis of urinary nitrogen offers additional information. In the earlier papers we have shown that an increase in the so-called residual nitrogen fraction is of frequent occurrence in all en-

TABLE V.  
NITROGEN PARTITION

Observation	I	II	III
Total Nitrogen.....(gms.)	6.43	7.81	2.31
Urea Nitrogen.....(%)	79.5	77.6	78.8
Uric Acid Nitrogen.....(%)	1.5	2.1	3.5
Ammonia Nitrogen.....(%)	4.3	5.4	4.3
Creatinin Nitrogen.....(%)	4.5	4.7	1.4
Residual Nitrogen.....(%)	10.2	10.2	12.0
% of cases with residual = or over 9%	33	67	100

doocrine and certain non-endocrine conditions. Further, one of us (18) has demonstrated that this increase is ascribable, in part, to the presence in abnormal amount of substances usually occurring in but very small quantities. In addition, however, there remains a moiety which is unaccounted for by the increase of known constituents and which patently must be referable to the presence of unknown nitrogen containing substances. We shall touch on this point again in the consideration of the blood chemistry. Several other observers have recorded either the presence of increased amounts of normal or the appearance of abnormal constituents, but the contradictory opinions seem to exist about these as well as the general protein metabolism. Our figures show an average for the series superior to the established normal, exceeded only by that for thyroid and with more than half of the cases exhibiting significant increase above normal. The percentage values of the several other constituents accord well with accepted standards. The absolute nitrogen elimination is, however, significantly low. Reference to the composite group of the other endocrinopathies already mentioned shows an average of substantially 9 grams as against the adrenal value 17 per cent lower. Since these figures were derived from a study of the urine nitrogen partition alone, and not from protein

metabolism experiments, no inference can be drawn as to retention. The patients were observed under the same conditions of liberal varied diet as were the other members of the series. That they show a characteristically lower nitrogen elimination for whatever cause, and that the partition formula departs from normality, may be regarded as indicated.

The results from the determination of certain blood constituents are given in Table VI.

TABLE VI  
BLOOD CHEMISTRY

Observation	I	II	III
Non-Protein Nitrogen.....(mgm.)	42	37	34
% over 35 mgm.....	100	44	0
Urea Nitrogen.....(mgm.)	17	16	11
% over 17 mgm.....	33	22	0
Uric Acid.....(mgm.)	3.4	3.6	3.3
% =or over 4 mgm. (net) *.....	0	11	0
Creatinin.....(mgm.)	1.5	1.5	1.5
Residual Nitrogen.....(mgm.)	23.3	19.2	21.3
Sugar.....(mgm.)	86	88	112
% under 80 mgm.....	33	22	0

\*All demonstrated cases of nephritis deducted.

†Value doubtful from emotional element.

The non-protein nitrogen shows an average level distinctly in excess of the usually accepted normal, the more strikingly as the urine indicates a low level of protein metabolism. Blood urea, on the other hand, is a high normal, while blood creatinin and the average uric acid concentration is normal, the latter in spite of the presence of the several cases of nephritis. Similar findings have been recorded in experimental animals, though again a word of caution must be expressed as to the interpretation of results with the moribund subjects of acute experiments. Blood chemistry values are profoundly influenced by the fatal experimental conditions. In the work of Marshall and Davis (19) certain observations would not seem to be affected by this objection. In our own cases representing the chronic as opposed to the acute condition, the non-protein nitrogen and uric acid in many of them indicate the characteristic relations of early nephritis first reported by Chace and Myers (29). The point of greatest significance is found in the residual or undetermined fraction. The average value here far exceeds the usual normal limits assigned by convention ( $15 \pm 2$  mgm.), and is even more marked in relation to our other groups.

It will be remembered in the discussion of the urine findings that the residual nitrogen fraction was found to be increased above the normal level. It was pointed out that this condition was not peculiar to adrenal involvement (the thyroid exhibits the anomaly in even more striking degree), but was shown generally in all endocrine and a fairly large group of non-endocrine disorders. As we see it, the observation rests upon an

end result of a rather wide range of metabolic disturbances, and is, at present, wholly non-specific. That the composition of the increment is a constant either qualitatively or, in relation to individual components, quantitatively, is hardly to be conjectured. Rather it is a single observation summing a large number of individual aberrations into a seemingly common end result. Further study on the character of this fraction and the variation of the amounts of individual components, may prove to be of real diagnostic import. While the urine findings present an outward

TABLE VII  
RESIDUAL NITROGEN IN BLOOD

Non-Endocrine . . . . . (500 cases)	15.2 mgm.
Pituitary . . . . . (400 cases)	15.1 "
Thyroid . . . . . (200 cases)	15.2 "
Gonad (Ovary) . . . . . (200 cases)	15.3 "

general unity, the blood in the adrenal cases offers a definite difference from the other endocrine entities. The blood of decapsulated animals has been frequently demonstrated to possess an inherent toxicity [Levin (21)]. This could arise from either of two causes, i.e., failure to remove poisonous wastes normally detoxicated by the gland, or synthesis of toxic materials as the result of disturbed metabolism resulting from ablation of the adrenals. A third alternative, lowered resistance, would not necessarily connote a change in blood composition. The present observation could be adduced to support either of the first two explanations. With our present ignorance of the complete composition of that fraction of blood nitrogen in health, it is impossible at the present time to hazard even a reasonable speculation. As Folin has emphasized, the determination of the qualitative and quantitative composition of this moiety of the blood constituents offers great possibilities, both to the physiologist and the diagnostician.

The remaining observation, that of blood sugar, is also of great interest. That hypoglycaemia occurs both in Addison's disease and with decapsulated animals, has been frequently recorded. In passing it may be said that the recording of blood sugar levels far below the convulsive threshold does not excite unlimited confidence in the actual numerical values. Low blood sugar, however, has come to have an accepted diagnostic value, and reference is frequently made to it. In the present series, the average is much lower than for any of the other endocrine groups, and in 25 per cent of the cases fell below the conventional normal lower limit of 80 milligrams.\* This fact, like the incidence of glycosuria already recorded, will be considered later under the general carbohydrate tolerance.

\*This statement does not take cognizance of the lower levels produced by the progressively more refined methods recently published by Benedict (22) and by Folin (23). Both writers agree that the lowest figures obtainable by a dependable method give the truest picture of the actual blood sugar level. As all of the measurements here reported were made by the well known Folin-Wu method, only standards based upon it may serve as criteria. The relative values remain unaltered.

The study of the form elements of the blood (Table VIII) yields results that in the main harmonize with current thought. While a variety of abnormalities are recorded in the literature, they are largely mutually contradictory. A secondary anaemia in the later stages and a more or less established lymphocytosis are the sole points of common agreement. The latter finding appears in our observations most strikingly in Group I; the former is missing from Group II as these cases were not in the terminal phase at the time of study. We observe a slight upward tendency of the eosinophilic elements, as has been recorded by others, although the point is one of those of debate. The picture, on the whole, is one of normality, barring the lymphocytosis and the anaemia of the Addisonians. The serological tests were uniformly negative.

TABLE VIII  
BLOOD MORPHOLOGY

Observation	I	II	III
Haemoglobin..... (%)	77	87	85
Erythrocytes... (1,000,000)	3 84	4 65	4 84
Color Index.. . .	1 0	0 93	0.88
Leucocytes..... (1,000)	6.9	7 9	6.3

DIFFERENTIAL COUNT

P. M. Neutrophiles . . . (%)	31	59	65
% = or over 75% . . .	0	11	0
Lymphocytes..... (%)	61	33	30
% = or over 33% . . .	100	33	0
Eosinophiles..... (%)	2	2	5
% = or over 3% (net)*. . .	33	22	100
Endothelial Leucocytes.... (%)	6	6	0

\*All cases deducted which present non-endocrine causes of eosinophilia.

In the next table will be found the results of the respiratory metabolism studies and certain concomitant observations.

The general consensus of opinion would seem to indicate that adrenal failure determines a downward tendency to the basal metabolic rate. Exceptions to this have been noted,\* but in the main, dependable data show decrease which in some cases, at least [Muirhead (24)] assumes a very tangible magnitude. The animal experiments recording the converse of this were in some cases, at least, not controlled for superimposed effects such as movement. Conceivably, the species also might play some part. The calorogenic action of adrenalin has been measured by Boothby and Sandiford (25) and their interpretations are confirmed by Graefe (26) in his recent monograph. This latter observation does not implicitly settle

\*Boothby and Sandiford (4) in their series showed one case with a rate above +20 per cent, while nine were within the normal range, only three falling below —10 per cent.

the question, since two glands are involved, but certainly does not negative a drop in basal rate from lowered adrenal function. In our own series the values ranged from  $-5$  per cent\* to  $-32$  per cent; the net average (12 cases) being  $-17$  per cent. Following the general method of presentation of Boothby and Sandiford, we have 4 between  $\pm 0$  and  $-10$  per cent, 4 between  $-11$  per cent and  $-20$  per cent, 2 between  $-21$  per cent and  $-30$  per cent, and 1 below  $-30$  per cent. As stated in the table, one case was omitted. The patient was a psychoneurotic woman, very restless and unable fully to co-operate. Several measurements were made, the best being 4 per cent above prediction but this test was unsatisfactory and the observed rate significantly above the truth. Several of the other cases were

TABLE IX  
RESPIRATORY METABOLISM

Observation	I	II	III
Basal Metabolism*			
Deviation..... High..... (%)	-10	†-5	
Low..... (%)	-21	-32	
% below prediction.....	100	100	
Average.....	-17	-15	-29
% between +10% and -10%.....	0	33	
% =or below -10%.....	100	67	100
Temperature..... Avg..... (deg.)	98.1	97.9	98.8
Blood Pressure			
Systolic..... Avg..... (mm.)	90	†96	90
% =or under 110 mm.....	100	89	100
Diastolic..... Avg..... (mm.)	54	†59	52
% =or under 65 mm.....	100	89	100
Pulse..... Avg.... (per min.)	75	74	94
Respiration..... Avg.... (per min.)	16	13	27
Alveolar Carbon Dioxide..... (mm.)	38	36	34
% under 40 mm.....	100	100	100

\*One case (psychoneurotic) omitted from Group II. See text.

†Febrile temperature 99.1°.

‡One case with long-standing cardio-renal disease and slight hypertension omitted.

probably not basal, and one had a slightly febrile temperature. As with the gonad cases where a similar inhibiting condition obtains, the values secured have been reported as they are representative of the results obtained with this group of patients. In the main it may be said that the severity of the condition is reflected in some measure in the degree of depression of the basal rate. This is not rigorously true, however, as the asthenia leads to a nervous instability and to restlessness.

The characteristic hypotension recorded by many others is here definitely present. The average systolic falls below 100 mm. and individual observations of less than 90 are recorded. The slightly increased pulse is not clearly displayed, but again this may be referable to the phase of the disease represented. Certainly the average indicates no downward tendency. The respiration rate confirms the conclusion offered above, as the lowered rate is observed only in the terminal phase.

\*Average of comparisons with both Harris-Benedict and Aub-duBois predictions.

We did not observe the hypothermia which is said to be characteristic of the condition. A temperature of 97° F. is the lowest recorded in the series, while one is slightly above 99°.

Alveolar carbon dioxide is a low normal. This is probably more apparent than real, as the asthenia of the condition makes it difficult to secure a really representative sample. The value recorded is undoubtedly a minimum, but equally, is probably representative.

The last observation to be recorded in this portion of the report is the Carbohydrate Tolerance, (Table X).

The findings here are diametrically at odds with the usually expressed opinion on the influence of the adrenal on sugar tolerance. There is a particularly voluminous literature in this field, and all writers seem to concur in the opinion that adrenal failure produces an increase in the

TABLE X  
GALACTOSE TOLERANCE

Group	Normal	Observed	Deviation
I Addison's Disease			
B-133.....	40	5	-87%
B-325.....	30	20	-33%
B-977.....	40	20	-50%
			Average -53%
II "Hypo-Adrenalism"			
B-62.....	40	50	* +25%
B-144.....	40	30	-25%
B-155.....	30	20	-33%
B-182.....	40	30	-25%
B-323.....	40	20	-50%
B-421.....	30	5	-83%
B-440.....	40	10	-75%
B-505.....	40	10	-75%
B-567.....	30	10	-66%
			Average -45%
III Pubertas Præcox.....	20	20	± 0

\*See text.

tolerance. The great majority of the studies from which this opinion derives, are based upon the influence of epinephrin injections on the level of blood sugar or, less frequently, on the appearance of glycosuria, procedures outside the range of this discussion. Of the very few studies which correspond with the present investigation, Eppinger, Falta, and Rüdinger (27), state that they found a very high tolerance for glucose in three cases of Addison's disease. Mussio-Fournier (28), examining the urine, found a high tolerance for glucose in one atypical case, while numerous writers have reported the low blood sugar curves which are interpreted as indicative of an increased assimilation limit. In only one paper, that by Forschbach and Severin (29) in which blood sugar curves were the criterion, has the writer been able to secure any evidence of a contrary observation. In this latter paper, one case of Addison's disease is reported with glycosuria after the test meal, while this case and one other show a significant rise to the blood sugar curve. The paper as a whole, however,



comparable to any of the others. A full protocol with discussion will be given later in the paper. Of the remaining twelve, three were clear-cut demonstrated cases of Addison's disease with pigmentation, six were seemingly functional failures with half of them possibly incipient Addisonians, and the remaining three were of an even more doubtful adrenal etiology. As, in the main, they have conformed to the general picture defined by the more authentic cases, and further, as thorough study failed to disclose any other cause for their presenting difficulties we have felt warranted in their inclusion.

The authors desire to repeat, perhaps redundantly, that they are acutely conscious of the short-comings of this series. Only the Addisonians are certainly cases of adrenal disease and they are but three in number. Their several pictures are consistent in detail, however, and may be adopted as criteria for the discussion of the larger number of assumed functional cases. Consideration of these latter is felt to be permissible in view of the many serious observers who avoid a guileless acceptance of the more extreme synthetic correlations of speculative endocrinology and yet concede the possibility of a lowered functional activity of the adrenal glands. The existence of accessory medullary and cortical tissue in other portions of the body with the possibility of local involvement, offers additional ground for conceiving such a condition to be possible.

One other point should be noted. With so brief a series as the present, statistical analysis is not highly significant. Agreement with the results of the more extensive surveys of others offers some slight support for the possible accuracy of the diagnosis; difference emphasizes only the limited amount of our material.

Without further preamble, we may undertake a brief clinical analysis of the cases.

The sex incidence of the disease is usually stated as equal or with a slightly greater frequency among females. In the subdivisions of the present series, the females are twice the number of males.

The ages can be presented in tabular form.

TABLE XI

## AGE AND ONSET

<i>Decade</i>	<i>Number</i>
21-30 .....	6
31-40 .....	2
41-50 .....	2
51-60 .....	0
61- .....	2

On the whole these values are in harmony with the usual record which places the years from 20 to 40 as those of greatest frequency. Late cases are known, however, the disease having appeared after the age of

80 in a few of those reported. Our three Addisonians were respectively 32, 48, and 61 years of age.

The time of onset in these three cases varied from three to twelve months before admission to the Clinic, with an average of nine months. As all of them have since died, the duration of the disease is known. Subject B-133, the youngest, had been sick for about one year at the time of admission and died almost exactly three years later (see Protocol in Part III). Subject B-977 exhibited an acute condition which began three months before our contact and ended three months later. The third Addisonian had been ill for one year prior to admission and lived for three years and one month after our study.

Of the functional group, five had been ill for less than four years, and one each reported severally 5, 10, and 25 years' duration. The last of these, subject B-323, referred her condition to some trauma to the coccygeal region at that time.

The family histories were particularly irrelevant, only one patient reporting tuberculosis, and one malignant neoplasm in fairly close relatives. Two others reported diabetes, the only endocrine condition cited, in reasonably near relatives.

The previous illnesses can be presented best in tabular form.

TABLE XII  
PREVIOUS DISEASES

Measles .....	11	92%
Whooping Cough.....	8	67%
Mumps .....	7	59%
Chicken-pox .....	7	59%
Influenza .....	5	42%
Pneumonia .....	2	17%
Trauma to Coccyx.....	2	17%

While none of the Addisonians had a previous history of tuberculosis, three of the functional group had positive histories of earlier involvement, and in two of the others it was probable although no active process could be demonstrated at the time of study.

Two of the patients in the second (functional) group had a history of some trauma to the coccygeal region, possibly significant in view of the accessory tissue normally found there.

Seven of the twelve had had one or more tonsillectomies, a proportion in accord with the incidence of tonsil disease already noted in the other endocrinopathies.

The chief complaints, as presented by the patients, are instructive.

Asthenia was offered as a major difficulty by eleven, and the twelfth case gave it as a minor symptom. The three patients with Addison's dis-

ease all complained of their pigmentation, and four of the functional group exhibited pigment changes of lesser magnitude in the skin.

Five of the group reported nervous instability as a principal symptom, and all of them exhibited it in significant degree.

TABLE XIII  
CHIEF COMPLAINTS

Asthenia .....	11
Pigmentation .....	3
Nervous Instability.....	5
Gastro-Intestinal Disorders.....	3
Pain .....	4

In this connection, a few words may be apposite in regard to the personality changes engendered by this disease. Analogous alterations have already been commented on in our papers on the thyroid and the gonads. While a psychical asthenia accompanies the physical fatigability, it does not determine an apathy in environmental reaction. Sufferers from Addison's disease are highly emotional, irritable, and the victims of apprehensions and needless worries. Perspective is lost on the affairs of life, and annoying or disconcerting trifles assume the magnitude of major calamities. Mental depression is noted much more frequently than the reverse. They differentiate, however, from the sullen truculency of the hypothyroid subject and the shrill self-insistence of victims of gonad failure.

Gastro-intestinal disorders were of primary importance to two, and in addition, six more complained of poor appetite, flatulency, and other evidences of impaired function. Five were constipated, and one had persistent diarrhoea.

Pain was a common finding and in four assumed major importance. It was rarely delimited as to site, but was usually found in the abdomen in every case as well as in other portions of the body.

The asthenia, pigmentation, and gastro-intestinal symptoms are frequently referred to as the triad of cardinal symptoms, while the other two are of usual occurrence. The frequency of representation of them in this group lends some support for the diagnosis in the assumed functional cases. While they may all derive from numerous other causes, some of these latter had been excluded by other parts of the study. Further, the symptom complex was but one evidence among the many, by the integration of which the diagnosis was established. We have already emphasized the necessity of regarding each diagnostic factor as significant only in its correlation with the general picture made up of many other independent measurements and observations. The agreement of our findings with those generally accepted as significant of adrenal disease, does not establish

a diagnosis but adds supporting evidence to the possible accuracy of our interpretation.

The majority of the patients showed an excessive susceptibility to infections of the respiratory tract, as shown by the data already recorded and by the fact that half of them reported very frequent colds (4), coryza (4), sore-throats (5), and kindred conditions.

Several of the group were subject to vertigo, and a number gave a history of fainting spells. Five complained of frequent and severe headache. Several had had otitis media in earlier years, and two showed a definite impairment of hearing. Nocturia was noted in 50 per cent, and intermittent polyuria in two patients. In the previous section the objective evidences of kidney involvement has already been emphasized. A true nephritis would seem to be even more frequently an accompaniment of adrenal disease than is the lowered permeability simulating nephritis of the thyroid failure.

The menstrual history of the eight women shows a relative normality.

TABLE XIV  
MENSTRUATION

	<i>Increased</i>	<i>Amount Normal</i>	<i>Diminished</i>
Irregular . . . . .	1	0	2
3			
Regular . . . . .	0	4	1
5	—	—	—
Total . . . . .	1	4	3

All of those showing irregularity had an increase in the interval, and with those of the entire group where the flow was not normal, the tendency was toward diminution. This is in harmony with the usual record of lowered exocrine activity of the gonads in adrenal disease.

A second supporting, if indirect, evidence is found in the marital histories of the group.

Only three of the twelve were married, two women respectively five and seven years, and one man whose married life extended over nearly forty years. Each of these unions had been productive of but one child, and there was no history of miscarriages. The direct data on libido were too meager to be significant, but the record given above may be regarded as possibly suggestive. In all of the other endocrine groups, including that of the gonad failures, the percentage of marriages is very much greater.

The physical examination yielded relatively few significant data.

Loss of weight and emaciation are usually predicated for adrenal disease. Three of our twelve patients were above their predicted weight, and of these one was the Addisonian in whom the disease ran a rapid course. This latter fact probably accounts for the anomaly. She was

underweight at the time of her death. The remaining nine were all below their predicted weights although three of them were still within the conventional normal limit of —10 per cent. The six remaining subjects averaged 22 per cent below their normal weight, and one of these (not an Addisonian) was 36 per cent below the calculated normal.

As has been noted above, 59 per cent of the group were pigmented in a greater or less degree. Several of the remainder were sallow, and only one exhibited a really healthy color of the skin. This was the patient (Case B-144) who was one of the doubtful group.

The hair presented nothing remarkable, there being no instance of a recognized deepening of color or marked anomaly in amount or distribution. Five of the patients had frankly poor teeth, and the dentition of several others was in but fair condition. As already noted, some patients had had tonsil operations, the tonsils of the remainder were normal.

One female patient had a slight thyroid enlargement; at the time of examination none exhibited adenopathy though several had an earlier history of enlarged glands. Four patients gave evidence of past or present pulmonary disease, and three showed abdominal tenderness. Five exhibited diminished reflexes. The remaining features of the examinations were not substantially significant.

Of the special examinations but few excite comment. Four of the patients gave evidence of apparently earlier pulmonary disease and the pyelograms of two of the Addisonians showed destruction in the upper portion of the kidney.

The eye examination demonstrated 75 per cent to have enlarged blind spots, but only 25 per cent showed yellowish discs. In only one case was there a significant contraction of the fields, and this was in one eye, the patient suffering from iritis in the other.

Neurological examinations confirmed the findings of the routine report, while none of the other observations threw light on the potential endocrine condition.

In the main it may be said that the members of the functional group gave pictures varying in degree rather than in kind of involvement from those of the Addisonians. As has been noted, the three established cases of Addison's disease differed from each other in certain respects, as one would naturally anticipate, and the majority of the functional cases showed no greater variation from conventional standards. No attempt has been made to review the literature as the few points of note in the clinical picture of this rare condition are matters of too general agreement to require debate.

Following the practice of the earlier papers in this series, the next section will be devoted to presenting the individual details of certain of the more representative and interesting cases in the form of protocols.

## PART III.

## CASE PROTOCOLS

The significant laboratory data of the first group are given in tabular form.

TABLE XV.  
ADDISON'S DISEASE

Observation				
Case Number.....		B-133		B-977
Date.....	Jan., 1924	Feb., 1924	May, 1924	April, 1928
Interval.....(mos.)	—	1	3	—
Sex.....	F	F	F	F
Age.....(yrs.)	32	32	32	48
Height.....(cm.)	162	162	162	158
Weight.....(kgm.)	51.8	50.2	50.0	61.4
Weight Deviation.....(%)	-8	-11	-11	+10
Lung Volume Deviation.....(%)	-28	-29	-28	-42
Basal Rate Deviation.....(%)	-6	-10	-13	-21
Blood Pressure.....(mm.)	104/62	90/54	108/70	90/58
Pulse.....(per min.)	94	74	76	86
Temperature.....(deg. F.)	97.2	98.4	97.6	97.1
Alveolar CO <sub>2</sub> .....(mm.)	31	35	36	40
Urine Volume.....(cc.)	2150	730	1800	720
Specific Gravity.....	1.013	1.025	1.015	1.014
Albumin.....	+	+	0	+
Casts.....	0	+	0	+
Sugar.....	0	+	0	0
Total Nitrogen.....(gms.)	13.58	8.37	15.13	6.13
Residual Nitrogen.....(%)	2.4	7.1	11.2	7.2
P. S. P. 2-hour Elimination.....(%)	79	62	—	42
Non-Protein Nitrogen.....(mgm.)	40	39	42	43
Uric Acid.....(mgm.)	4.3	3.4	4.2	3.5
Sugar.....(mgm.)	80	75	80	99
Haemoglobin.....(%)	90	85	90	75
Erythrocytes.....(1,000,000)	5.52	4.28	4.61	3.81
Color Index.....	0.82	0.99	0.98	0.98
Leucocytes.....(1,000)	8.2	8.7	6.8	8.3
Neutrophils.....(%)	45	17	33	39
Lymphocytes.....(%)	42	73	59	50
Eosinophiles.....(%)	1	4	2	3
Endothelials.....(%)	12	6	6	8
Misc.....(%)	0	0	0	0
Galactose.....Normal.....(gms.)	40	40	40	40
Observed.....(gms.)	—	5	—	20
Deviation.....(%)	—	-87	—	-50

## GROUP I. ADDISON'S DISEASE.

**CASE B-133. (CHRONIC)** The patient's chief complaint was of pigmentation of the skin coupled with a marked asthenia. Since early childhood, she had presented several dark brownish moles on the face and a large irregular naevus-like dark pigmented area on the lower anterior half of the left side of the neck. Two years previously she noted an increase in the number of moles on her face, and one year previously a general darkening of the skin, most pronounced on the face, hands, and a band surrounding the middle of the body. The asthenia she dated from an attack of the grippe about a year previously, so that the pigmentation and weakness showed substantially the same chronology.

**Family History:** The father died at the age of 38 of diabetes. There were three living sisters and three others who had died in childhood of acute infections.

*Past History:* The patient reported the minor ailments of childhood, tonsillitis every year until a tonsillectomy six years earlier, and in addition, the attack of grippe already mentioned. She had had no association of which she was aware with tuberculosis. The other significant points in the history were abscessed ears ten years previously, teeth requiring much dental attention, and an occasional gastro-intestinal disturbance characterized by flatulency, distress, and nausea. She had had occasional fainting spells, and at times numbness and tingling in the hands. The patient was unmarried, established the catamenia at the age of 14, and gave an entirely normal menstrual history.

*Physical Examination:* She was a fairly well developed, poorly nourished woman, 32 years of age. The exposed surfaces showed a peculiar copper colored appearance which during the examination was also observed in a broad irregular girdle about the waist. The other portions of the body were also brownish but less strongly pigmented. The naevus on the neck was remarked, and numerous brown moles on face, neck, and arms. The lips were somewhat pigmented, as were the gums and small areas of the buccal mucosa. Examination of the lungs showed a questionable increase in intensity of the breath sounds at the left apex, and a few dry rales heard throughout both lungs. There was slight tenderness in both costal vertebral angles, a fine tremor of the hands, and a bluish color of the nails. No evidence of cardiovascular disease was detected.

*Laboratory Summary:* The urine volume was somewhat high; there was a trace of albumin. The elimination was excellent, the protein intake ample, and the partition formula normal. The blood morphology was normal except for a marked lymphocytosis. The blood showed an increase above the normal of all of the nitrogenous constituents, and a blood sugar at the low level of the normal. The vital capacity measurements showed the patient to be 8 per cent underweight, and with a significant loss from the predicted lung volume. The basal rate was recorded as —6 per cent, with low blood pressure, rapid pulse, and slightly sub-normal temperature. This value of the basal rate was not regarded as accurate since the patient was slightly nervous.

*Radiography* of the chest give normal findings, but an indefinite shadow was remarked above the upper pole of the left kidney.

*Skin Examination:* The observer at this time commented on the suggestion of Addison's disease, felt that mineral poisons and a chloasma of toxic origin must also be considered, and recommended a biopsy.

*Discussion:* Feeling that the observations available were too limited to warrant a final diagnosis, and desiring to study the patient more thoroughly in the hope of resolving the condition, she was admitted to the Hospital a few weeks later and a much more complete study was undertaken. The interval history was irrelevant.

*Second Examination:* The urine volumes were found to be somewhat low, and the urine contained albumin, sugar, and granular casts. Her protein intake had decreased although it was still above a maintenance level. The residual nitrogen fraction showed a definite upward tendency although still within the conventional normal limit. The blood showed a marked increase in the lymphocytes and a 4 per cent eosinophilia. There was evidence, for the first time, of a slight degree of anaemia, with a color index of one. The blood chemistry values were somewhat lower for the uric acid, the high non-protein nitrogen remained unchanged, while the blood sugar had sunk below the conventional normal limit. The 'phthalein test, though still normal, had fallen off somewhat. The patient had lost 1.6 kgm. weight. The lung capacity was substantially unchanged. The basal rate was 10 per cent below prediction, and again the measurement of the observed rate was undoubtedly somewhat above the truth. A sugar tolerance test was performed with galactose, and it was found that the assimilation limit was greatly depressed, even so small a dosage as 5 grams being enough to produce a transitory appearance of galactose in the urine. The alveolar carbon dioxide was still low, an observation ascribed in part to the patient's weakness, with consequent difficulty in collecting a representative sample.

*Neurological Examination* gave entirely normal findings throughout.

*Pelvic Examination* gave normal findings.

*Radiography:* The skull and sella were normal. An area of calcification in the falx cerebri was reported. The chest was negative, and the radiogram of the abdomen failed to confirm the shadow near the kidney which had been

previously recorded. Some density of the right mastoid cells was noted, the sinuses were otherwise normal.

*Eye Examination:* The discs were yellowish in color, the blind spots slightly enlarged; the remaining findings were normal.

*Urea Curve:* The data showed a depressed elimination, both qualitatively and quantitatively.

*Biopsy:* A biopsy was performed and the excised tissue was subjected to careful examination by Dr. A. M. Greenwood. The portion from the naevus was reported by him as characteristic of the tissue from which it was taken. The second section, which was excised from another part of the neck, showed only increased pigment in the basal layer, which, with special staining, was demonstrated to be melanin.

*Discussion:* The patient's history and her presenting symptoms were naturally suggestive of Addison's disease. There were further in the literature a few records of lowered basal rate in this condition in man, perhaps the most significant of which were the records of Muirhead (24) from the Mayo Clinic, and those of Aub (30) and his associates. The reports from several laboratories of increased basal rate in experimental animals with injury to these glands was not regarded as significant since the animals were not in a basal state. On the other hand the injection of adrenalin is known to increase the respiratory metabolism. The patient's sugar tolerance represented a sharp divergence from the few existing records in the literature. This has already been discussed earlier in the paper. The patient presented evidence of lowered kidney permeability, the low blood pressure and blood sugar generally associated with Addison's disease; certain of the other possibilities such as primary anaemia and bronzed diabetes were practically eliminated by certain of the other observations. On this basis a tentative diagnosis of Addison's disease was established and medication instituted.

The clinical features of particular interest were the absence of demonstrable foci of tuberculosis elsewhere in the body, the albumin and casts in the urine, the evidences of depressed renal function furnished by the blood chemistry, phenolsulphonphthalein test, and urea curve, and the character of the asthenia.

The impression still persists that non-pulmonary tuberculosis is practically always associated with the pulmonary form, and that a diagnosis of non-pulmonary tuberculosis rests on insufficient evidence if the former is not demonstrable. While it is true that autopsy usually shows some evidence of pulmonary involvement in those patients exhibiting the disease elsewhere, it is more often than not impossible to demonstrate the association clinically. Therefore absence of pulmonary tuberculosis demonstrable by clinical methods should not deter one from making the diagnosis of the disease elsewhere in the body.

Albumin and casts were present in the urine of the majority of our patients with Addison's disease, and were generally accompanied by other evidences of disturbed renal function. (See table XV.) Such findings, generally significant of nephritis, should not be allowed to direct one's attention away from possible adrenal disease if they are accompanied by significant hypotension and asthenia of the characteristic type. If pigmentation is present there is little danger of this, but if there is no pigmentation, as happens, according to Falta (9), in nearly one-third of the cases, undue emphasis upon the urinary findings may decoy one away from the true diagnosis.

The character of the asthenia in our patients with Addison's disease has been so typical that its main features seem worth emphasizing. Although there is usually complaint of constant lack of energy, the feature peculiar to adrenal destruction has been the sharp exacerbation of weakness upon effort and its rather rapid remission when effort ceases. The patient under discussion furnished a clear example. She was a school teacher and was able to carry out most of her tasks without distress, although she was very weary when the day's work was over. An attempt to lead the class in a short and easy "setting up drill," however, would almost always produce a feeling of profound weakness, accompanied by dyspnoea, trembling, and frequently nausea. Ten or fifteen minutes rest would result in complete disappearance of this asthenic condition, leaving her "practically as good as she was before." This cycle of events which seems to lend supporting evidence to Cannon's emergency theory is, in our experience, typical of Addison's disease (if severe cardiac disease be excluded), and is of fundamental importance in distinguishing it clinically from other conditions causing asthenia.



In April the patient returned for a basal metabolism test which showed a level of  $-5$  per cent under what seemed to be satisfactory conditions. The blood pressure had risen to 112, and the patient apparently was much improved. In May a series of observations was made (see table) which may be briefly reviewed.

The urine was again ample in volume, as in the beginning; albumin, sugar and casts had disappeared; the elimination was excellent. The appetite had improved, and the protein intake was almost double that of February. The residual nitrogen, however, had increased to a point significantly above the conventional normal. The blood still showed a marked lymphocytosis but definitely lower than that recorded in February, while the eosinophilia had returned to a normal value. Both the red count and the haemoglobin were somewhat increased, and there was no secondary anaemia. The blood sugar showed an increase to the initial low normal level. The nitrogenous constituents, however, had also increased to substantially their initial value. The patient's increased protein intake undoubtedly contributed something to this. The weight was substantially unchanged, as was the vital capacity. The basal rate was now 13 per cent below prediction, with the blood pressure slightly above that of the first record and significantly superior to that of the second.

*Radiography:* An x-ray plate taken at this time raised a question of a possible area of increased density in the mid-portion of the right wing of the sacrum.

The patient was continued under medication throughout the summer, and in the fall resumed her occupation which she had earlier been obliged to discontinue. She had gained three kilograms in weight. The blood pressure maintained the advantage shown, and her general condition showed a definite improvement.

The Muirhead treatment, modified as symptoms indicated, had been faithfully followed. But the patient was extremely sensitive to adrenalin, and its administration was omitted early since it seemed to do more harm than good. Cortical substance was, however, well tolerated, and the subjective symptoms became much less marked during its use. The patient carried on her work as a teacher with very little discomfort, and her "setting up drill" now rarely caused more than moderate fatigue. From time to time she had sudden attacks of abdominal pain and nausea, rarely causing vomiting, but on the whole her condition was excellent and her energy sufficient.

During the Christmas holidays of 1927 she caught cold. In spite of it she returned to work two days later. She showed no untoward effects from the "cold" when she started for school in the morning, but on reaching home in the afternoon she complained of the abdominal pain previously mentioned, and of difficulty in breathing. Her physician was summoned and found her in a state closely simulating surgical shock. The extremities were cold; pulse small, rapid, and feeble; breathing rapid, shallow and labored. No evidence of pneumonia could be found. She grew worse very rapidly. The breathing was described by her physician as being "like that of an over-etherized patient," and it soon became necessary to hold the jaw forward to prevent strangulation. She became unconscious and died, apparently of respiratory failure, within eight hours after returning to her home, on foot.

We were fortunate in securing an autopsy and are indebted to Dr. Charles F. Branch for his skillful services in this connection. The skin over the entire body was of a peculiar dark brownish tinge, the lungs were normal except for a well defined edema, the liver gave evidence of recent parenchymatous degeneration, and the right ovary showed two small simple cysts on the upper surface.

*Kidneys:* *Left:* The approximate weight was 150 gms., it was firm, smooth, regular, and bright reddish-brown in color. The cut surface disclosed a normal relationship between the pyramids and cortex, the latter measuring about 6 mm. in width, the entire surface being markedly injected, and upon scraping yielding a slightly blood-tinged purulent material on the knife edge. The capsule stripped with ease, leaving a markedly injected surface. The pelvic epithelium was not injected. *Right:* Was similar in every respect to its fellow on the left. *Microscopic Examination:* Many of the tubules were completely desquamated, while in others the epithelium was swollen and coarsely granular; the cytoplasm and nucleus took a uniform pink stain. The lumens contained varying amounts of coagulated serum, epithelium and debris. The glomeruli were engorged and stained poorly. The vessels throughout were engorged; there was moderate general increase of connective tissue throughout which in places was infiltrated with, and showed accumulations of leucocytes. Occasional

sclerosed glomeruli were noted. The connective tissue about the pelvis was edematous.

*Adrenals:* After diligent search in the region where the adrenals should have been, on either side was discovered some small compact masses of pale white tissue, seemingly fibrous in character, which were preserved as sclerosed adrenals. Upon examining the cut surfaces of these masses absolutely no evidence of any structure resembling adrenals, was observed. *Microscopic Examination:* Absent on either side and apparently replaced by a mass of tissue which upon microscopical examination appeared to be enlarged sympathetic ganglia.

From the clinical standpoint the most interesting features of this case are the long duration of the disease after the diagnosis was established and the considerable improvement under treatment, which is astonishing in the light of the autopsy findings, and the character and brevity of the final stage, suggesting that a very small fraction of the total adrenal tissue may be sufficient to support life, but that even a mild infection may overwhelm the patient.

**CASE B-977 (ACUTE).** The patient's chief complaint was of a brown coloration of the skin, coupled with a marked degree of asthenia. Three months previously the patient's mother had died, the event producing a profound emotional shock. Following this she became very weak and began to lose weight rapidly. A few weeks later she found herself unable to continue her employment. She developed an attack of grippe, and during her convalescence noted that her skin was becoming brownish in color. During the three months of the course of her complaint she had lost 25 lbs. The weakness and pigmentation had both been progressive. Five days before admission she had had a single attack of vomiting without well defined cause.

*Family History:* The mother died following an operation for hernia at the age of 75, and the father at the same age of cerebral hemorrhage. The remaining family history was entirely irrelevant.

*Past History:* Beyond measles at three, diphtheria at 13, and a tonsil operation at 38, the patient's history was relatively uneventful. She had always been healthy and a steady worker. Her teeth had been removed for pyorrhea. She stated that a year and a half previously, after an attack of epigastric pain, a diagnosis was made of duodenal ulcer, and under medical advice she had been on a bland diet since that time. The menstrual history was entirely normal up to six months ago, but in this interval she had missed three periods. As the patient was 48 years of age she ascribed this to an approaching menopause. She reported a slight tingling sensation in the right hand occasionally, and a slight skin eruption on the arms after eating tomatoes. There had been no association with tuberculosis.

*Physical Examination:* The patient was a well-developed, well-nourished woman of 48. There was a bluish-brown pigmentation all over the body, most marked on the exposed surfaces. The patient was apathetic and appeared fatigued. There was apparently some loss of hearing in both ears. The buccal mucosa was pigmented, the chest apparently normal, the radial arteries were slightly firm. Routine neurological findings were substantially normal except for somewhat poor pass pointing.

*Laboratory Summary:* The urine was somewhat scanty and it contained albumin and a very few hyaline casts. The elimination was poor. The protein intake was below a maintenance level, and the residual nitrogen showed an upward tendency although within the conventional normal limit. The blood morphology showed a lowering of both haemoglobin and leucocytes, and a normal color index. There was a marked lymphocytosis and a 3 per cent eosinophilia. The blood non-protein and urea nitrogen values are definitely above the normal level, while the blood sugar was normal. The 'phthalein output was definitely low, and the urea index below the normal. The patient was 10 per cent overweight but nearly 50 per cent below her predicted lung volume, a finding probably referable to her asthenia. The basal rate was 12 per cent below prediction, with definitely low blood pressure, and, at the time of the test, a somewhat rapid pulse. Later evidences seemed to indicate that the basal rate, as recorded, was probably distinctly above the truth, and that the real rate was between 20 per cent and 30 per cent below prediction. The value recorded in the table, derived from a second test, was —21 per cent, and this was still probably somewhat high. The patient's sugar tolerance was half the normal level.

*Chest Examination* gave no evidence of disease.

*Endermal Skin Tests* gave no evidence of protein sensitivity.

*Liver Function (McClure)* determination indicated normal biliary function.

*Orthopedic Examination:* Moderately pronated feet were the only abnormality recorded.

*Skin Examination:* The appearance was regarded by the examiner as typical of Addison's disease.

*Radiography:* A series of gastro-intestinal plates showed a constant defect consistent with duodenal ulcer. There was some degree of visceroptosis. The skull and sella were normal, heart and lungs normal, and a plate of the lower leg where the patient had a tender spot showed no abnormality.

*Cardiogram* gave normal findings except for a relatively low voltage consistent with the patient's adynamic state.

*Audiogram* showed normal hearing.

*Cystoscopic Examination* gave normal findings.

*Eye Examination:* The discs were yellow and the fundi showed slight vascular sclerosis and a generalized tessellated pigmentation.

*Urea Curve:* Was normal in shape and gave evidence of good elimination.

*Levulose Tolerance* was much depressed.

*Icteric Index and Van den Bergh* reactions indicated normal function.

*Pyelograms:* The right renal pelvis was dilated; the calyces blunted. The left kidney was of the spider type.

*Discussion:* The whole general picture here was felt to be consistent with Addison's disease in a somewhat acute state. The lowered sugar tolerance, while not in accord with other reports in the literature, was consistent with our own observations. The Muirhead treatment was initiated, the patient remaining under observation in the Hospital. One month after beginning treatment a satisfactory basal rate showed a level only 4 per cent below prediction, with distinctly low blood pressure (88/52) and a slightly rapid pulse. The patient's condition did not improve, however; the asthenia was progressive and complicated by sensations of pain which were not exactly localized but seemed to be confined to the body. Toward the end of the second month the patient's failure became more rapid, and early in the third month after admission, death supervened. An autopsy, the details of which we owe to the courtesy of Dr. Charles F. Branch, showed bilateral pulmonary tuberculosis and Addison's disease.

*Adrenals:* The left weighed 24 grams. It was slightly injected and had a distinctly firm, woody feel, was coarsely nodular and the surface, instead of showing the customary fine mottling of the cortex, was almost a uniform dull, pale yellow. The surface showed no normal landmarks remaining, the cortex and the medulla being completely absorbed in a coarsely mottled, yellow and reddish gray mass, with not infrequent small islands of calcification present. No caseous material was observed, per se, although many areas simulating it were seen with the naked eye. The adrenal of the opposite side was similar in every respect to its fellow on the left. *Microscopic Examination* showed that the normal histological architecture of the organ had been completely replaced by a mass of amorphous, caseous material. This was surrounded by a thick fibrous capsule, infiltrated with a large numbers of endothelial cells and lymphocytes.

Except to emphasize its similarity to the previous case, there is little to add from the clinical point of view. The picture of impaired renal function was similar to that already discussed. The bilateral pulmonary tuberculosis was obsolete, and gave no evidence of its presence by either roentgenologic or clinical methods of examination, supporting our previous statement that inability to demonstrate pulmonary tuberculosis during life is not an argument against the existence of a non-pulmonary infection.

CASE B-421. The patient was a young man whose chief complaint was of constant glycosuria for the past five years, associated during the same interval with intermittent periods of profound fatigability. He was disposed to date the initial onset of his condition from an attack of influenza nearly 7 years previously, following which he had an attack of severe mental depression and a gen-

eral slowing up of psychomotor activity. The condition passed in a few weeks but had recurred at intervals. Five years ago, following one of them, he consulted a physician who found several per cent of sugar in the urine. A diabetic diet improved his general physical condition but did not render him sugar free. Three years ago he entered a hospital and was put on a starvation diet for six weeks with a resulting loss of 40 pounds in weight, but again without rendering him sugar free. Throughout his entire period the attacks of mental and physical depression had recurred, usually lasting from one to two months and with a gradual recovery.

TABLE XVI  
"HYPOADRENALISM"  
GROUP II. "HYPOADRENALISM"

Case Number.....	B-121	B-182	B-323	B-505	B-567	B-940
Sex.....	M	F	F	F	M	F
Age..... (yrs)	22	22	40	26	25	68
Height..... (cm)	175	163	165 5	154 5	165 5	160 5
Weight..... (kgm)	64 1	31.8	60 6	41.8	52 0	51 8
Weight Deviation..... (%)	-6	-36	-1	-12	-3	-2
Lung Volume Deviation..... (%)	-8	-29	-2	-23	-15	-45
Basal Rate Deviation..... (%)	-32	-18	-18	*-11	-16	+5
Blood Pressure..... (mm.)	114/72	92/54	90/50	88/58	85/66	108/62
Pulse..... (per min)	64	73	54	88	76	87
Temperature..... (deg F.)	98 0	98 6	97.2	98 0	97 4	97 0
Alveolar CO <sub>2</sub> ..... (mm)	39	31	39	39	37	42
Urine Volume..... (cc)	1450	1680	1050	540	610	400
Specific Gravity.....	1 039	1.005	1 013	1.025	1 020	1 020
Albumin.....	+	+	+	+	+	+
Casts.....	+	0	+	+	+	+
Sugar.....	30	0	0	0	+	+
Total Nitrogen..... (gms)	14.73	4 24	7 29	6 02	5.70	4 92
Residual Nitrogen..... (%)	11 0	5.7	13 3	10.1	18 0	13 8
P. S. P. 2 hours..... (%)	61	26	48	35	55	26
Non-Protein Nitrogen..... (mgm)	47	36	35	35	26	41
Uric Acid..... (mgm.)	4 8	2 9	3 6	3 3	2 0	5.3
Sugar..... (mgm.)	85	93	93	76	85	111
Galactose... Normal..... (gms)	30	40	40	40	30	30
Observed..... (gms)	10	30	20	†20	10	20
Deviation..... (%)	-67	-25	-50	-50	-67	-33
Haemoglobin..... (%)	100	95	70	70	80	75
Erythrocytes..... (1,000,000)	5 36	5 12	4 21	3 55	4 02	4 40
Color Index.....	93	93	82	.99	1 00	85
Leucocytes..... (1,000)	9 3	5 9	6 7	8 4	10 8	19 2
Neutrophils..... (%)	58	58	75	62	58	82
Lymphocytes..... (%)	28	32	24	29	37	8
Eosinophiles..... (%)	3	0	1	2	2	0
Endothelials..... (%)	10	10	0	7	3	10
Misc..... (%)	1	0	0	0	0	0

\*True rate lower

†Test incomplete Tolerance possibly lower.

**Family History:** The mother had a renal disorder which had led to three therapeutic abortions after she had borne four children, of whom the patient was the third. All of the siblings had died in early infancy. Cases of tuberculosis, cancer, and diabetes were recorded in grandparents and great grandparents; none in the immediate generations.

**Past History:** The patient's birth history showed a normal delivery but a very long labor. Development was entirely normal. At the age of six he had measles, and this was followed by an abscess in the neck and what was said to be a spot in the lungs. The chest condition apparently cleared up in about two years. He further reported minor ailments, diphtheria at the age of nine, and a severe attack of influenza at 15 with a very slow convalescence. He grew very rapidly between the ages of 13 and 15. He also had a tonsillectomy at 14, and trauma to the head at the age of 8 which apparently produced only surface injury. The regional history showed frequent earaches in childhood, soft teeth requiring much dental attention, constipation, but was otherwise not remarkable. There was a history of a fairly active sex life with no venereal infection.

*Physical Examination:* The patient was a well developed and fairly well nourished young man of 22. His teeth showed much dental attention, the chest was normal; there was a slight tremor of the fingers, rather abundant hair growth of normal distribution, and somewhat hyperactive knee jerks.

*Laboratory Summary:* The urine volume was normal, elimination and balance good. An average content of 30 grams of glucose was reported; the remaining findings were normal. The nitrogen partition determination showed an adequate protein intake and a high residual nitrogen fraction; the blood morphology was substantially normal; there was a marked increase in the level of the nitrogenous constituents, and a low normal blood sugar. The 'phthalein test and alveolar CO<sub>2</sub> were normal. The patient was 6 per cent underweight and of substantially normal lung capacity. The basal rate was 32 per cent below prediction, with normal blood pressure and slightly low pulse.

*Adrenalin Test:* Injection of adrenalin produced a definite increase in the blood sugar level from 82 to 122 mgm. with a gradual subsidence, the level being 100 mgm. at the end of two hours. There was a progressive leakage of sugar through the kidney.

*Radiography:* The skull and sella were entirely normal.

*Neurological Examination:* There was no evidence of organic nervous lesion. The examiner remarked that the pupils were widely dilated, and that after light stimulus there was a slight contraction followed by immediate dilatation.

*Audiogram:* Definite loss of hearing, except in the higher register was noted.

*Eye Examination:* The blind spots were slightly enlarged. The findings were otherwise normal, the examiner failing to confirm the anomalous pupillary reaction noted above.

*Discussion:* The general picture here presented was in some measure consistent with a disturbance of each of two independent endocrine glands, namely, the adrenal and the pituitary. The basal rate was of the order of adrenal or thyroid failure, but the latter is practically excluded by the patient's sugar tests since no other evidence presented of any additional cause for his depressed tolerance. In hyperpituitary cases, hypertension, and evidences of hypertensive nephritis are not infrequently found, but they are associated with an over-activity of both lobes. While most adrenal cases present a markedly lowered blood pressure, we have seen one case with an associated kidney involvement which exhibited a hypertensive level. On the basis of the markedly lowered sugar tolerance, the definitely lowered basal rate, the suggestion of renal disturbance conveyed by the picture of the blood chemistry, the patient's general history, the unimpaired libido, and a number of other generally supporting evidences, it was felt that diagnosis of functional hypoadrenalism was warranted to the point at least of undertaking experimental medication.

We have been fortunate enough to keep this patient under supervision, and have had opportunities for checking certain of the laboratory findings at not infrequent intervals. During the year 1926 a number of such observations were made, but at the end of this time the patient had so far improved from the clinical standpoint that the frequent checks were omitted. Early in 1928 the patient reported and the improvement previously noted was found to have persisted. Certain of the more significant data can be reduced to tabular form and discussed independently.

TABLE XVI-a  
RESPIRATORY METABOLISM

Date	B. M. (%)	B. P. (mm.)	T. (deg.)	Wt. (kgm.)	Dev. (%)
2-1-26	—32	114/72	98.0	64.1	—6
13-2-26	—7	118/60	97.4	63.8	—7
1-7-26	—11	116/64	97.8	63.6	—7
26-10-26	—26	108/66	97.4	64.6	—6
11-12-26	—23	110/64	97.6	64.9	—5
21-3-28	—18	108/70	98.0	70.1	+2

Inspection of the table shows an improvement in the basal rate to a substantially normal level within the course of a few weeks, and this was maintained with but slight variation for another five months. Following this the summer vacation intervened, and in the fall the patient was found to have lost

on the basal rate and to have slipped back nearly to his earlier level. That he had not been assiduous in following his treatment was freely acknowledged. The blood pressures follow the same general trend, the body weights remain fairly constant. Although medication was intermittent following the last test in 1926, the patient had gained in weight and improved somewhat in his basal level when seen in 1928.

The next table

TABLE XVI-b  
BLOOD CHEMISTRY  
Values in mgm. per 100cc. blood.

Date	N. P. N.	Urea N.	Uric Ac.	Creat.	Residual	Sugar
2-1-26	47	23	4.8	1.5	21.8	85
13-2-26	42	22	4.7	1.5	17.8	91
1-7-26	43	21	3.9	1.5	20.1	99
26-10-26	38	18	4.2	1.5	18.0	95
11-12-26	32	15	4.7	1.6	14.8	86
21-3-28	36	19	4.7	1.6	14.8	86

shows the changes in the blood chemistry, and here the improvement is very striking. The diminution in the residual nitrogen fraction to a sustained normal level is certainly significant. The rise of blood sugar during the early period of active treatment was also interesting. The blood uric acid was favorably affected as well, but at the time of the last examination it had returned to its original level. A few of the urine sugar values are given in the next table.

TABLE XVI-c  
URINE DATA

Date	Vol. (cc.)	Sugar (gm.)
2-1-26	1450	30
1-7-26	1660	16.6
26-10-26	2550	74
11-12-26	1430	71.5
21-3-28	1620	70.6

The lowering of the sugar elimination and its return to a much higher level when dietary restrictions were removed, is obvious from the figures given.

During the period of observation in 1926 a cardiogram was secured which showed a normal organ.

Clinically, it is impossible to furnish sufficient supporting evidence for the diagnosis of "hypoadrenalism" in this case. It is even impossible to state what that evidence should be, since there exists no proven symptom pattern of the condition. There is no doubt, however, that the patient has a definite endocrine disturbance, and the more important symptoms coincide more nearly with those of adrenal impairment, as evidenced in early Addison's disease, than with any other condition known to us. The intermittence of the subjective symptoms is not consistent with the dead level of energy deficiency characterizing thyroid and pituitary deficiency. The undiminished libido would be an enormous stumbling block for any one desirous of explaining the picture on the basis of hypogonadism. The lack of neurological findings renders "pique" diabetes improbable. And finally, the subjective and objective response to treatment is suggestive, though by no means convincing evidence, that the working hypothesis is correct. Similar responses to treatment have recently been reported by Koehler (31), but we do not share his belief that they can be regarded at present, as an adequate therapeutic test. We are reporting these cases of "hypoadrenalism" because it seems desirable to add to the evidence for or against such a condition rather than because we believe its existence proved.

CASE B-182. The patient's chief complaint was of fatigue and indigestion. She dated the latter from an attack of "ptomaine poisoning" which had occurred some 4 years previously, and which was characterized by abdominal pain, nausea, vomiting, and diarrhoea. Six months later the same group of gastrointestinal symptoms reappeared and had continued intermittently up to the time of her admission for the study. She had lost 17 pounds during this interval but had been underweight at the time of its onset. The condition had been accom-

panied by a marked fatigability which ultimately obliged her to discontinue her occupation which was clerical in nature. At about the time that the symptoms began, brownish pigmented areas developed on the face. These have persisted although there has been some variation in their intensity.

*Family History* was irrelevant.

*Past History:* The patient reported minor ailments and influenza at the time of the epidemic. Some time after the onset of the present condition a gastrointestinal x-ray study was carried out which yielded only negative results. In spite of this the patient was placed on an ulcer diet for some time without improvement in her symptoms. She complained of an occasional headache, poor appetite, and flatulency. The menstrual history showed a normal onset, some irregularity with increase in the interval, and a very scanty flow over periods of seven days. Beyond an occasional ache in the lower limbs, the remaining history was entirely irrelevant.

*Physical Examination:* The patient was a poorly developed and distinctly emaciated girl of 22. A slight dullness at the apex of the right lung and increased vocal fremitus on the right side were reported. Pigmented areas were noted. The right knee jerk somewhat below the normal activity; the remaining findings were normal.

*Laboratory Summary:* The patient was 36 per cent underweight and had lost nearly one-third of her predicted lung volume. The basal rate was significantly below prediction, and the observed value was somewhat above the truth, as the patient's breathing was very irregular and the trend of the curve not exactly determined. A later measurement showed a value of about —23 per cent, and there was some doubt if this also were truly representative. The blood pressure was at a distinctly hypotensive level; the alveolar carbon dioxide below a normal level. The urine volume was ample but the elimination very poor. Albumin was recorded; no casts were observed. The protein intake was definitely below a maintenance level and this would undoubtedly tend to lower the observed basal rate. The blood nitrogen values were relatively high in view of the low level of protein metabolism. The blood sugar was normal; the sugar tolerance somewhat depressed; the blood morphology was substantially normal.

*Radiography:* A gastro-intestinal study showed ptosis of the stomach, but conditions otherwise normal. The skull was normal. The left lung showed fibrosis apparently due to an old infection, while the right lung was normal.

*Neurological* findings were normal.

*Pelvic* findings were normal.

*Eye Examination:* The patient showed much enlarged blind spots but otherwise normal conditions.

*Discussion:* Viewed from the endocrine standpoint, the thyroid could be eliminated by both subjective and objective evidences. With a lowered sugar tolerance and basal rate there is a suggestion of pituitary dysfunction which the enlarged blind spots might be adduced to support. The relative degree, however, of abnormality in these two tests did not conform with the usual pituitary formula. The combination is likewise found with the gonad failure, and here the low alveolar carbon dioxide might be regarded as a supporting evidence. That this low level was in part due, however, to an inability of the patient, through asthenia, to perform the test properly, robs the actual level of something of its authority. With the patient's poor nutrition one would infer a tendency not to lower but to raise the sugar tolerance, on the basis of lack of saturation of the tissues in accordance with Folin's theory. We have observed such a change in under-nourished patients without endocrinopathy who promptly came to a normal level after a short period of proper feeding. There seemed to be no evidence of active tuberculosis, although this again was not rigorously excluded. The patient's asthenia was disproportionate in degree to that observed in pituitary or ovarian cases of a like degree of severity, as indicated by the objective measurements. On this basis a diagnosis of hypoadrenalism was offered tentatively and the experimental application of the Muirhead treatment recommended. The patient was referred from another city. We lost contact with the case and are ignorant of the outcome. While there are several evidences here which are more consistent with a functional adrenal deficiency than with that of another endocrinopathy, we regard this case as distinctly doubtful.

**CASE B-323.** The patient's chief complaint was of continuous backache, nearly constant headache, abdominal pain, and marked asthenia. In 1900, 25 years earlier, the patient received a severe blow on the coccyx, probably fracturing it. From this time she dates her backache. The coccyxgeal condition was not recognized for over a year, and then operation was regarded as unwise. Coincident with this trauma she developed an obstinate constipation. The menstrual function, which had been normal up to that time, became very irregular, with shortened interval, very profuse flow, and marked dysmenorrhea. After a long ineffective course of ovarian medication, surgery was invoked and a double salpingectomy, uterine suspension, and appendectomy were performed. Following this she became markedly asthenic, developed attacks of syncope, and the menstruation became very scanty; there was no improvement in her general condition. Still later a plaster jacket was applied to the spine and the backache was somewhat better during the period of its use. She was next given a vaccine treatment for arthritis, and finally a diagnosis of mucous colitis was offered. The backache has continued and is seriously inhibiting. She required special arrangements of pillows in her bed in order to lie with any degree of comfort. Latterly she has experienced formication in the lower extremities, also cramps, and deep muscle and bone pains. The onset of her headache was coincident with the initial trauma; it grows worse during the day and is increased by menstruation. It presents the anomaly that the headache subsides in some measure as the flow becomes more profuse. The abdominal pain was situated in the left lower quadrant and came on in the late afternoon. It was of short duration and at times so severe as to produce vertigo. The patient's fatigability has been progressive but is less marked in the morning. At times she is forced to lie down, and while she does not sleep and is conscious of people and of sounds, she is unable to rouse herself. A number of years previously she developed the morphine habit from the therapeutic use of the drug, but the condition was speedily corrected.

*Family History* disclosed no relevant details.

*Past History:* In addition to the episodes noted above, the patient recorded the usual children's diseases, abscessed ears and tonsillitis. She had had a tonsillectomy and a dilatation and curettage. She believed that the salpingectomy was performed because of a tuberculous condition of the tubes. The remaining history, including that of the menses, was not remarkable.

*Physical Examination:* The patient was a well developed and nourished woman of 40. The lips were somewhat cyanotic, the teeth widely spaced. The chest was apparently normal. There was a vague tenderness over the entire abdomen not really localized although possibly increased over the right kidney and in the right lower quadrant. There were brownish pigmented areas on the exposed surfaces, marked tenderness over the coccyx and sacro-iliac region, and a small cystic tumor at the level of the 12th dorsal vertebra over the spine which was not tender. Body hair was heavy but of normal distribution.

*Laboratory Summary:* The patient's vital capacity measurements were normal. The basal rate at a sub-normal level, with low blood pressure, slow pulse, and slightly sub-normal temperature. The CO<sub>2</sub> output was normal. The urine volume was normal; elimination poor; both albumin and casts were reported. Protein intake was somewhat low. The residual fraction of the urine was definitely above the normal. The 'phthalein test gave a borderline value. The blood chemistry was normal. Sugar tolerance was at half the predicted level. There was a distinct secondary anaemia, and the blood was leucoid in type.

*Endermal Tests:* The patient was not responsive to a large number of proteins.

*Radiography:* The coccyx showed a left lateral deviation. The skull was normal as were the spine, sacrum and hips. The caecum was irregularly filled, the appearance raising a question of pylorospasm.

*Orthopedic Examination:* This confirmed the tenderness over the sacro-iliac region and determined a possible moderate relaxation of the joints. The small tumor growth was designated as a lipoma which was of no importance in the patient's case.

*Pelvic Examination* gave normal findings.

*Eye Examination:* Findings were normal.

*Audiogram:* Showed substantially normal hearing.



*Neurological Examination:* No organic nerve lesion was disclosed.

*Discussion:* The condition of the coccyx and lower back seemed to account for her backache. The defect in the function of the caecum could possibly have resulted from adhesions arising from her previous operation. It could also be due to a tuberculous condition, and the questionable pylorospasm could also be referable to either of these causes. From the endocrine standpoint, with a lowered basal rate and lowered sugar tolerance, a pituitary dysfunction, ovarian failure, and adrenal failure were all possibilities. The blood pressure was somewhat low for a pituitary failure; likewise, the blood uric acid was normal and there was no eosinophilia. The eye grounds were normal and there were yet other evidences which rendered a pituitary disorder improbable although not excluding it.

A primary ovarian failure can not be so readily excluded. It is true that the menstrual function showed irregularity and profusion, but the analysis of a long series of ovarian cases shows this particular formula to be the least common. The patient exhibited a definite anaemia, and this we have not observed to be the usual finding in ovarian failure although one to be expected when the adrenal is involved. The normal alveolar carbon dioxide, the leucoid blood, and distribution of body hair, are not characteristic of ovarian failure. As direct supporting evidence for the adrenal, the very low level of blood pressure, the marked fatigability, the evidences of renal impairment, may all be enumerated. The exposed surfaces were somewhat pigmented, and enquiry elicited the fact that none of her family showed a similar coloring. The normal blood sugar is by no means characteristic, but the patient was acutely sensitive to pain and nervously unstable, and this level might represent a slight response to the emotional stimulus which could be engendered in even hypofunctional adrenals. The patient had apparently had tuberculosis in the pelvis, and where tubes are thus involved there are usually other tuberculous areas. On the whole, while the case could not be regarded as clear cut, enough evidence presented to warrant a tentative diagnosis of functional hypoadrenalism. The Muirhead treatment was recommended and was followed for a short time after the patient returned home, with distinct evidence of improvement. It was subsequently discontinued and indirectly we have learned that the patient has relapsed into her earlier condition which is continuing adversely.

Here again is a case in which the main evidence to support the diagnosis is the response to treatment. We have already stated that we do not believe the therapeutic test convincing proof, but it seems worth while to record the findings, as only in this way will enough evidence be accumulated to clear up the very indefinite situation as regards "hypoadrenalism."

Clinically, there was certainly a large element of nervous and emotional instability in this patient, and the time honored diagnosis of neurasthenia can be rejected only because it fails to explain the objective findings. We believe that in this and many other instances the neurasthenia is the result, not the cause, of the metabolic disturbances, and that an attempt at their normalization is at least an essential part of the treatment of patients presenting, in addition to evidences of disturbed metabolism, signs of nervous instability. But we wish to make clear our belief that convincing demonstration of metabolic disturbance is an indispensable pre-requisite to such treatment.

**CASE B-505.** This is an incomplete case but the evidences are highly suggestive. The patient's chief complaints were of fatigue and fainting spells, tinnitus, and nausea. The patient had been married six years previously, having been well up to that time. Her baby was born five years ago. She failed to regain strength after confinement, and she dated her present condition from that event. She reported that she slept well but was always fatigued, the latter condition progressing during the day. The attacks of nausea developed two years previously and without any predisposing factor so far as the patient could tell. There was no vomiting; there was occasional pain under the left rib border, also low in the abdomen. The onset of the fainting spells was coincident with the nausea, and recently the patient had developed severe attacks of vertigo. The tinnitus was a recent manifestation. Two years ago she learned that her blood pressure was very low.

*Family History:* Two of three siblings died in early infancy.

*Past History:* The patient had one or two of the minor childhood diseases and scarlet fever. At the age of 5 she fractured her nose, producing a unilateral obstruction. A few weeks earlier there had been a severe blow to the head but

radiograms of the skull showed no structural injury. She reported an occasional sensation of swelling in the upper eyelids, soft teeth, some chest pain, dyspnoea and palpitation. The bowels were regular but she was troubled with flatulency. The menstrual function had been entirely normal up to 2 years ago when for a period of one year she exhibited shortened intervals.

*Physical Examination:* The patient was a poorly developed and nourished woman of 26, ambulatory but seeming very weak. Obstruction of the right side of the nose and poor teeth were noted. The pulse rate was somewhat rapid. There was some enlargement of the proximal interphalangeal points; the skin was dark without heavy bronzing, and pilosity on the extremities was marked. The eyebrows were bridged, and there was a slight mustache, also some hair on the breasts. The abdominal hair was heavy but of normal distribution.

*Laboratory Summary:* The patient was a small woman 12 per cent below her predicted weight and definitely below her predicted lung volume. An unsatisfactory basal rate determination showed —11 per cent with very low blood pressure and somewhat rapid pulse. Repetition of this test was impossible as the patient began to menstruate, returned to her home in another state, and was subsequently felt to be too weak to return for a completion of the study. This episode influenced the completeness of the entire investigation. The alveolar  $\text{CO}_2$  was normal. The urine volume was scanty, elimination fair only; both albumin and casts were reported. The protein intake was somewhat low, the residual nitrogen fraction high and the 'phthalein test definitely below the normal. The blood chemistry was fairly normal though the nitrogenous constituents showed an upward tendency in relation to protein intake. The blood sugar was below the normal level. The sugar tolerance was incomplete but was certainly 50 per cent below the normal, and from the amount of sugar excreted during the test probably at a still lower level. The blood showed a definite secondary anaemia without evidence of active degeneration; the leucocytic formula was substantially normal.

*Nose and Throat Examination:* The tonsils were apparently not offending. The nasal septum showed a sharp deflection to the right.

*Pelvic Examination:* Conditions were normal except for minor residua of child-bearing.

*Eye Examination* showed slightly enlarged blind spots; otherwise findings were normal.

*Discussion:* The whole general picture here is compatible with a condition of failure of the adrenals. The possibility of organic involvement was not excluded, but the incomplete character of the test robs a conclusion of any final authority. Muirhead treatment was recommended, but no further observation of the patient has been possible. Clinically the history is very suggestive of Addison's disease, including as it does the acute exacerbations of weakness and nausea found in our patients with proven adrenal disease.

CASE B-567. The patient's chief complaint was of a swelling of the legs and hips, with marked distention of the scrotum. For the past 10 years the patient had had a chronic arthritis with involvement of the right shoulder and the hips. For the past two years there had been extreme pain at night along the course of the sciatic nerve. For a period of a few weeks before admission there had been much swelling of the feet, while the enlargement of the scrotum had appeared two weeks earlier.

*Family History:* One uncle died of tuberculosis; the history was otherwise not informative.

*Past History:* The patient had the minor ailments of childhood, a tonsillectomy at the age of six, and removal of cervical glands three years previously. Six months earlier he had developed iritis of the left eye and had been under continuous treatment for this condition. Some four months earlier he developed a diarrhoea and the use of an acidophilus culture intensified his condition. Under other medication there had been some improvement but he was still passing three or four loose movements daily. He gave a history of a blow on the testicle during boyhood that caused a swelling which subsided spontaneously after lasting for several weeks. He experienced some formication on the legs at such times as they were swollen.

*Physical Examination:* The patient was a poorly developed man of 25, requiring the use of a cane when walking. The skin was covered with acne, there

was slight ptosis of the left upper eyelid, and the iris was cloudy; there was circumcorneal and conjunctival injection, also moderate photophobia with lachrimation. The right eye was normal. He exhibited herpes on the lower lip, the gums were pallid, and the teeth poor. The left chest was somewhat depressed, producing a definite asymmetry, and the left shoulder drooped downward and forward. The pulse rate was somewhat rapid, the blood pressure distinctly low. Beyond shallow respiration, the lungs were apparently normal. The scrotum was large and distended, and contained a large amount of fluid. The arms exhibited limitation of motion at the shoulder and at the right elbow, with some muscular atrophy. The knee joints were swollen and enlarged, tender, and limited in motion. From the knee down the legs were edematous. There was some bronzing of the skin on the lower extremities.

*Laboratory Summary:* The patient was slightly underweight and not significantly below his predicted lung volume. The basal rate as recorded was 16 per cent below prediction, with a normal pulse and very low blood pressure. Alveolar CO<sub>2</sub> was a low normal. The urine volume was scanty and the elimination poor. The urine contained albumin and sugar, while the sediment exhibited much epithelial debris and many granular and epithelial casts. His protein intake was inadequate; the residual nitrogen fraction was double the upper normal level. The 'phthalein output was low normal. The blood chemistry showed normal values entirely consistent with the level of the patient's protein metabolism. The blood sugar was low normal; the sugar tolerance, definitely depressed. The blood showed a slight secondary anaemia with an upward tendency to the leucocytes and a slight increase in the lymphocytes.

*Examination for protozoa:* Repeated examination at night failed to disclose the presence of filaria.

*Electrocardiogram:* The low voltage indicated an adynamic state consistent with adrenal disease.

*Cardiac Examination:* The heart was found to be normal. A very low blood pressure was recorded.

*Orthopedic Examination:* The patient presented generalized evidences of chronic arthritis in all stages of development. At the time of this examination the edema had affected the legs and the body as high as the second or third lumbar vertebra.

*Eye Examination:* The patient's left eye exhibited subacute inflammation, defined as kerato-iritis, with contracted pupil. The right eye was normal except for a slightly enlarged blind spot.

*Radioscopy:* Several abscessed teeth were demonstrated; both lungs were hazy, the left auricle prominent; the spine showed a general osteoporosis; there was destruction of the cartilage in both sacro-iliac synchondroses; the right shoulder showed atrophic arthritis; both knees a hypertrophic condition, while the left hip showed both atrophic and hypertrophic processes. The gastrointestinal appearances were normal.

*Chest Examination* showed conditions to be substantially normal.

*Dental Examination:* Several cavities and several infected teeth were demonstrated.

*Genitourinary Examination* disclosed no abnormality except the scrotal edema and that of the legs. The laboratory evidences did not show markedly impaired renal function.

*Stool Examination:* Ova and parasites were absent.

*Discussion:* A study of this case was felt to disclose the existence of two conditions which were by no means necessarily related. In the first place the patient had a definite arthritis of nearly ten years' standing, reported an earlier tonsillectomy, and exhibited a number of infected teeth. Second, there was evidence of nephrosis with edema, but without marked evidence of greatly lowered permeability. While asthenia was not stressed in the history, the patient was markedly fatigable and had been so for some time. The general laboratory picture accorded more nearly with that produced by adrenal failure than by any of the other endocrinopathies. A tentative diagnosis was offered of an early functional impairment of the adrenals. It is, however, recognized that the chronic focal infection, the arthritis, and the renal impairment, might account for most, if not all of the findings.

**CASE B-940.** This case is included because of the condition found at autopsy. The patient's chief complaint was of pain in the left side of the abdomen and the lumbar region. It had begun some three months earlier, had been progressively more severe and continuous, and was apparently unrelated to any event or habit of the patient's life. There had been a progressive loss of weight—some 40 pounds in the past three months—and a severe asthenia had developed.

*Family History* was entirely irrelevant.

*Past History:* The patient had had a few minor ailments in childhood, life-long weakness of the eyes following measles in this period, and one attack of influenza many years before. A tumor in the right breast had been successfully treated by electricity twenty years previously. She reported headache with nausea earlier in life; no attacks for many years. She was subject to rhinitis of a severe type. Though the patient was 68 years of age but few of her teeth had been removed. The appetite had been good until the development of the present illness. With its onset, however, she had developed nausea, flatulency, and diarrhoea. There was apparently an impairment in the sense of taste. Oliguria was a feature of the current complaint, previous to which, however, there had been nocturia. The patient matured early and the menstrual history was uneventful, including the menopause in the early fifties. In years past there had been a mild arthritis in the knees.

*Physical Examination:* The patient was a well developed woman of 68 showing evidences of much loss of weight. The pupillary reactions were very sluggish; the eyes showed incipient cataracts. There was some septum deviation and a moderate amount of crusting. The gums and teeth were in very poor condition. Smooth, firm masses were detectable over each clavicle, and there were several smaller masses in the neck. The heart gave a blowing systolic murmur, the pulse was slightly rapid. A large mass was felt in the left side of the abdomen with possibly other masses in the epigastric and left inguinal regions. There were several tumor masses on the left thigh, the largest of which suggested a lipoma. There were a number of brownish pigmented areas on the upper body and lower extremities. The knee jerks could not be elicited, and there was a positive bilateral ankle clonus. A generalized adenopathy in cervical, axillary, and inguinal regions was recorded. The distribution of the body hair was entirely normal.

*Laboratory Summary:* The urine volume was very low and the elimination very poor. Albumin and sugar were both present, while the sediment showed many leucocytes, hyaline, and granular casts. The basal rate was +5 per cent with a somewhat low blood pressure and rapid pulse. The temperature was slightly sub-normal; alveolar carbon dioxide, normal. The patient was 2 per cent under her predicted weight but had lost nearly half her predicted lung volume. Protein intake was low, residual nitrogen high, and the 'phthalein output much below the normal. The nitrogenous blood constituents were distinctly above the normal level. The blood sugar was a high normal. The blood showed a moderate degree of secondary anaemia, and a definite leucocytosis with increase in the neutrophilic elements.

*Laryngological Examination:* The tonsils were enlarged and infected; the teeth in very poor condition.

*Cardiogram:* There was some evidence of cardiac impairment of a degree not inconsistent with the patient's age.

*Radiography:* Numerous infected teeth were demonstrated, and several retained roots. The skull was thickened but was otherwise normal. There was a large tumor mass on the left side of the abdomen reaching below the iliac crest; an additional large mass in the pelvis which showed numerous calcium deposits. The gastro-intestinal tract was normal except for redundant colon.

*Eye Examination:* The left eye showed an old choroiditis with scars producing an irregular partial central scotoma; the right eye was substantially normal.

*Neurological Examination:* This confirmed the evidences of a spinal cord lesion previously recorded.

*Surgical Examination* confirmed the presence of a tumor mass in the abdomen and the generalized adenopathy. The large tumor on the left thigh was diagnosed as a lipoma.

TABLE XVII  
"PUBERTAS PRAECOX"

Observation	Sex—Female									
	4-29-1925	7-28-1925	10-20-1925	1-26-1926	4-27-1926	6-20-1926	10-19-1926	6-25-1927	7-5-1928	
Date.....	7-9	8-0	8-3	8-6	8-9	8-11	9-3	9-11	10-11	
Age..... (yrs.-mos.)										
Height..... (cm.)	115	121	122.5	124	126.5	127.5	129	134.5	141.5	
Weight..... (kgm.)	22.0	23.8	26.1	28.4	31.7	29.6	31.4	36.1	42.7	
Weight Deviation..... (%)	-3	-5	-2	+4	+12	+2	+3	+0	+10	
Lung Volume Deviation..... (%)	—	-51	-48	-38	-30	-34	-27	-28	-14	
Basal Rate Deviation..... (%)	-29	-10	-18	-8	-24	-18	-24	-28	-21	
Blood Pressure..... Svs.	90	92	100	90	84	86	100	92	116	
..... Dias.	52	58	58	55	48	40	55	50	64	
Pulse.....	94	102	100	92	90	84	84	77	86	
Temperature.....	98.8	99.0	98.8	98.8	98.2	98.6	98.2	97.6	98.6	
Alveolar CO <sub>2</sub> .....	34	37	38	42	42	39	33	43	42	
Urine Volume.....	480	850	550	620	570	330	740	560	640	
Specific Gravity.....	1.007	1.010	1.018	1.014	1.019	1.016	1.012	1.024	1.018	
Albumin.....	+	0	0	0	+	+	+	+	+	
Cast.....	0	0	+	0	+	0	0	0	0	
Sugar.....	0	0	0	0	0	0	0	0	0	
Total Nitrogen.....	2.31	4.45	4.90	4.92	4.68	3.30	5.02	5.62	5.10	
Residual Nitrogen.....	13.3	10.3	5.6	13.6	6.2	6.3	8.6	12.5	7.1	
P. S. P. 2-hour.....	53	63	60	68	62	63	55	45	60	
Galactose.....	20	20	20	20	20	20	20 ?	30	40	
..... Normal.....	20	20	20	10	10	10	30	30	40	
..... Observed.....	±0	±0	-50	-50	-50	-50	+50 ?	±0	±0	
Blood.....	34	31	33	—	28	33	26	27	32	
..... Non-Protein N <sub>2</sub> .....	3.3	3.1	4.0	—	3.8	4.2	4.6	2.6	3.3	
..... Uric Acid.....	112 ?	107	99	—	105	96	91	93	100	
..... Sugar.....										
Haemoglobin.....	85	95	80	95	85	100	95	85	80	
Erythrocytes.....	4.84	4.59	4.35	4.71	4.28	4.97	5.30	5.20	4.40	
Color Index.....	0.88	1.03	0.90	1.01	0.99	1.01	0.90	0.82	0.91	
Leucocytes.....	6.3	4.6	7.6	8.0	10.5	7.2	9.1	7.8	7.4	
Neutrophils.....	65	48	31	40	47	73	60	56	66	
Lymphocytes.....	30	40	60	45	43	21	30	37	29	
Eosinophiles.....	5	6	2	6	3	1	3	1	1	
Endothelials.....	0	6	6	8	7	5	7	6	4	
Misc.....	0	0	1	1	0	0	0	0	0	

*Orthopedic Examination* demonstrated arthritis in the knees and spine, with possibility of malignant neoplasm in the latter.

*Discussion:* The case was diagnosed as general carcinomatosis, which was naturally inoperable. She was retained in the Hospital and died some four weeks after admission. At autopsy a large hypernephroma of the left kidney was disclosed with numerous metastases to the lung, liver, and the entire abdominal, peribronchial, thoracic, and cervical lymph glands. The right adrenal was normal. The left was so closely associated with the left kidney that microscopically it formed an integral part of the mass. This case is reported as that of a patient with presumptive destruction of one adrenal and exhibiting certain of the evidences which may be associated with adrenal disease. The normal basal rate constitutes a definite exception, while the patient's alveolar carbon dioxide is higher than that of any other case reported in this group. We have demonstrated in other cases of malignant neoplasm that the sugar tolerance is definitely lowered. The patient had malignant involvement of one kidney, while the other gave evidence of definite nephritic changes. From the differential standpoint the normal basal rate, in spite of the patient's grave condition, rapid loss of weight and lowered nutritional level, is significant. It might be inferred that the value obtained was an algebraic summation of the depleting factors already noted and an upward tendency engendered by the adrenal involvement. This is, however, purely speculative, and in the writers' opinion highly improbable.

From the clinical point of view, it is interesting to compare the findings in this patient with those cited above, and the fact that her symptoms are very similar to those of the other individuals in this group is important. Certainly there could have been impairment of adrenal function in this last patient, and if her symptoms are ascribable to that condition it may fairly be argued that the similar symptoms of the rest of the group might likewise be explained. It is, however, not safe to go so far, since this last patient had an abdominal tumor large enough to bring about mechanically her digestive symptoms, while her asthenia, and many of the laboratory findings may be fairly referred to the general carcinomatosis. So far as our series of cases is concerned it must be said that the case for hypoadrenalism is "suspected but not proved."

### GROUP III. PUBERTAS PRAECOX

CASE C-16, et seq. The case of this little patient is reported because of its general interest and of a possible adrenal element. In our opinion this latter is far from established, although there are numerous references in the literature to an association of early puberty with certain types of adrenal disease. Many of these, however, lack objective supporting evidence, and this case is reported without prejudice and for consideration.

The child was admitted to the Hospital late in April, 1925, complaining of a gradually developing weakness of the arms and legs. As a matter of fact she was unable voluntarily to raise arm, leg, or even a finger. The condition dated back to May of the previous year when the child came home from school complaining of illness. After her arrival home she had a severe nose-bleed and vomited, but had so far recovered that she was able to return to school the next day although she complained of a severe headache. As the latter persisted she was kept at home and in bed for several days, during which the tongue became very yellow, and the child apparently temporarily lost the use of her legs. She again recovered from this in a few days but shortly afterward was hit in the right leg which caused her to limp for about three months. The right leg became progressively weak during this period and subsequently weakness developed in the left leg, in the hands, and in the arms. A tonsillectomy was followed by temporary improvement but the child then developed pneumonia some three months before admission to our Clinic. During her attack of pneumonia she was seen by a number of physicians whose opinion was divided between a condition of progressive muscular atrophy and of infantile paralysis. At the time of admission here there was complete inability as noted above.

*Family History* was irrelevant.

*Past History:* Beyond the facts already noted the patient had had chicken-pox and measles but otherwise up to the time of her illness she had been unusually well and strong. The catamenia had not been established.

*Physical Examination:* The patient was a well-developed and well-nourished child, seven years and nine months of age. She was unusually alert mentally.

and distinctly mature. The physical findings in the main were normal. The child had no prehensile strength in her hands. The arms could not be flexed at the elbows, nor could the legs and thighs. There was neither adduction, abduction, or flexion in legs and hips; the right leg was somewhat atrophied, and there was foot drop in both extremities. The knee jerks and wrist jerks could not be elicited; there was no ankle clonus. The Babinski and Oppenheim reactions produced flexion. There was abundant hair growth on the legs, arms and external genitalia. The skin was white and free from pigmented areas.

*Laboratory Summary:* The child was within 3 per cent of her predicted weight. The lung volume could not be ascertained. The basal rate deviation was 29 per cent below prediction. Too much weight should not be given to the absolute magnitude of this datum as standards for female children of this age are far from well established. The relative value, however, is significant when compared with the later measurements. The pulse was distinctly rapid, the blood pressure somewhat low. The urine volume was somewhat scanty, the elimination poor, and albumin was present. The total nitrogen showed an entirely inadequate level of protein metabolism. The residual nitrogen fraction showed an upward tendency. It is to be borne in mind that with lowered protein intake in the normal individual, the relative value of this fraction tends to increase. On the other hand, the patient was a seven-year-old child weighing but 22 kilograms, hence her protein level was not as low relatively as would be connoted by the same nitrogen elimination in an adult. The phthalein output was low normal. The sugar tolerance was normal. The blood nitrogen values were relatively high but within the conventional normal limits. The blood sugar was slightly high but this could have been due to an emotional response. The blood morphology showed somewhat low values throughout, the sole exception being a 5 per cent eosinophilia.

*Radiography:* The spine, pelvis and sella were normal; the skull somewhat rachitic in shape. The mediastinal shadow was 5.5 cm. in diameter. The heart and lungs were normal.

*Neurological Examination:* A fine muscular palsy affecting the lower extremities, pelvic girdle, and the shoulder girdle was observed. In the examiner's opinion the atrophy was absent which would be expected in a case of anterior-poliomyelitis. Final opinion was reserved.

*Discussion:* While the child had not established the catamenia, she had a marked growth of pubic hair and the body configuration suggested a beginning maturity. While, as noted above, too great weight could not be placed on the absolute value of the basal rate, it was evident that there was a marked lowering from the level to be predicted in health. The child was under proteinized, which could be a factor, but was not undernourished. There was evidence of a lowered kidney permeability. The child was definitely asthenic; on the other hand the sugar tolerance was normal. It was felt that the illness which the child had experienced had not been properly evaluated. It was impossible to get additional details but there seemed to be no question that the present condition had followed the somewhat vague attack described above. Many of the features were consistent with adrenal impairment, although a thyroid failure could not be excluded with certainty in view of the low basal rate and the normal sugar tolerance. The complementary features of a thyroid failure were, however, entirely lacking. On this basis a tentative diagnosis of adrenal dysfunction was offered and treatment by adrenal cortex suggested. Through the cooperation of the parents, the child was returned to the hospital some three months after our first contact. In the meantime she had been receiving adrenal cortex. It was found that there was a definite improvement in many ways. The whole general musculature had become much stronger, the child was able to raise hands, arms and legs when in a recumbent position. Some atrophy in the extensors of the hands with slight contractions on flexion; foot drop, and marked weakness in the extension of the toes were still apparent. A thorough neurological examination and review of the case, for which we are indebted to Dr. N. H. Garrick, ruled out anterior poliomyelitis and progressive muscular atrophy. In his opinion the vague illness which was the starting point of the whole condition could possibly have been an unrecognized diphtheria, and the muscular condition which was its sequel, a postdiphtheretic paralysis. From the laboratory standpoint the basal rate was found to have increased to the low normal borderline. The patient had grown 6 cm. and increased in weight 1.8 kgm. The pulse was slightly higher, the blood pressure practically unchanged; the alveolar carbon dioxide had increased to a low normal level; the urine vol-

ume had improved, as had the elimination; the protein intake was double, which naturally could have some influence on the improvement in the basal rate. The residual nitrogen fraction was lower, though still high, and the 'phthalein output had increased to a satisfactory normal level. The sugar tolerance remained unchanged. The blood chemistry had improved somewhat in spite of the increased protein intake. The blood morphology showed a slightly lower red count, a slight leukopenia, an increase in the lymphocytes, and a persistence of the eosinophilia. Adrenal cortex medication was continued, and three months later the child was tested again. The weight had improved, the basal rate had subsided to a point midway between the earlier records, sugar had appeared in the urine, the residual nitrogen had become normal, the sugar tolerance had dropped to a level below the normal, a slight secondary anaemia had developed, the lymphocytes had risen to 60 per cent of the normal leucocyte content, while the eosinophilia had disappeared. It is unnecessary to review all of the data of the repeated tests performed on this child in the table given above. Suffice to say that she has regained full use of her arms and hands, there is still a residual toe drop which is being gradually overcome under orthopedic correction. She can walk and run with considerable freedom. The sugar tolerance, while remaining at a depressed level for a period, in September, 1926, exhibited a marked increase to a point above the normal, which was interpreted as indicating an approaching onset of menstruation; this latter was established a few months later, when the child's tolerance became normal and has remained so up to the present time. Adrenal cortex was discontinued after the first marked improvement, and the child has progressed satisfactorily without recent therapeutic aid. The basal rate has remained low, the blood pressure has steadily improved to a present normal level, and the somewhat rapid pulse has given evidences of subsidence. The alveolar carbon dioxide has become entirely normal. The general normalizing of the other factors is apparent from the table. In view of the child's marked improvement it has been felt best to avoid further endocrine medication. She reports yearly to the hospital and a thorough study is carried out. In time it seems probable that it may be wise to resume endocrine therapy. The need for it at the present time, however, has certainly not been demonstrated.

As was stated in the beginning, we have no desire to be dogmatic about this case. It may be permitted, however, to indulge in some speculation, recognizing that it is no more than this. If we assume the accuracy of Dr. Garrick's diagnosis of an earlier diphtheria producing a post-diphtheretic paralysis, we have a patent explanation both for the initial muscular weakness, and equally for its gradual improvement with the passage of time. This, however, would fail to explain the child's early evidences of maturity, and might not entirely account for the very rapid improvement of the muscular condition during the initial phase of her therapy. If the adrenal be a detoxicating organ—and there are many who believe it so to be—it is conceivable that it had passed through a phase of over-stimulation as an incident to the toxæmia arising from the patient's diphtheria. Evidence would seem to indicate that with certain of the endocrine glands such a period of overactivity is followed by a compensatory lowering of functional level. That precocious puberty arises in an overactivity of the gland, is in no small measure assumptive. The presence of a tumor of the cortex does not necessarily connote a functional overactivity, but may imply the reverse. Be that as it may, it is possible that the early maturity of this little patient had its origin in impulses from changed adrenal function which in turn derived from the earlier toxæmia. It is interesting to note that the child's persistent thymus exercised no deterring effect on the progress of her maturation. The case is offered merely for consideration. Continuance of the study may, at some future date, throw light on the underlying etiology. That a thyroid element, as suggested by the present basal rate and sugar tolerance, could enter in, is entirely contrary to the very large number of existing records where thyroid failure at this age has produced a completely opposite effect. That vague and dubious entity, a hyperovarianism, can not be invoked, as at no time had the child shown an increased galactose tolerance with the exception of one observation shortly before the onset of menstruation, and here the fault unquestionably lies with the definition of the standard, and the patient's tolerance was consistent with the physiological stadium. A pituitary factor could find some support, as the child has shown irregularly an eosinophilia, a high blood uric acid, lowered basal rate, and a lowered sugar tolerance. In a long series of pituitary cases, however, we have never studied a patient who showed so marked a depression of the basal rate while exhibiting a normal sugar tolerance. Pituitary cases, transitional between an initial hyper-



and terminal hypo-activity of the posterior lobe, may be studied fortuitously, while the sugar tolerance is passing through the normal zone. We have observed a few such cases, checking the accuracy of the initial inference by subsequent study of the case after the transition has been completed. While the anterior lobe seemingly undergoes involutional activity to a hypofunctional level more readily and rapidly than the posterior lobe, we have never observed a case in which the anterior lobe has been so far ahead of the posterior in its transitional adjustments. Finally, a stimulating influence on the genital sphere is observed in overactivity, not failure, of the pituitary. The case for the pituitary then would seem to lack substantial support, and we feel constrained to conclude that if the patient be endocrinopathic the adrenal would seem to be the most probable focus of involvement.

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# THE RELATIONSHIP OF IODINE TO THYROID HYPERPLASIA AND FUNCTION\*

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The literature upon thyroid disease is so voluminous, the ideas expressed are so varied and many of the papers are so abstract that physicians who have not made a special study of goiter are more confused after reviewing the literature than before beginning such a study. It is time for those who are making an actual study of the thyroid and its pathology to sift carefully the wheat from the chaff and state in a definite, clear and concise manner the present status of our knowledge.

The clinician's interest in goiter centers around three major problems. First, the insuring of a normal thyroid gland at birth; second, the prevention of goiter; and third, the treatment of goiter in those patients in whom it has been permitted to develop.

Halstead in 1896 stated that congenital goiter could be produced by the removal of a greater portion of the thyroid gland of a pregnant female dog, but that the removal of a major portion of the thyroid gland of the male had no influence upon the thyroid of the progeny. Experimental work has confirmed Halstead's observation. A study of the patients with congenital goiter whom I have seen in private practice and in the goiter clinic of the University of Oregon has led me to the conclusion that congenital goiter in the human is of exactly the same origin. That is, if the mother's thyroid gland is not secreting enough thyroxin during pregnancy, a demand is thrown upon the child's thyroid gland to function in utero. As the result of this demand, there is either a secretion of colloid resulting in a colloid goiter, or a hyperplasia resulting in one of the types of hyperplastic goiter. Congenital goiter thus produced is not then an hereditary disease, but is instead a congenital condition developing as a compensatory process. So true is this that whenever we see a family in which all or nearly all of the children have goiter, we can with practically a hundred per cent of accuracy predict that the mother had a goiter, and although the thyroid gland may have been able to produce sufficient secretion under ordinary conditions, it was deficient when the added load of pregnancy was thrown upon it. I have yet to see the first patient with congenital goiter borne by a woman with hyperthyroidism, and I do not believe it occurs. By that, I do not mean to say that a woman who has a deficient thyroid during pregnancy may not as a result of the stimula-

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tion thrown upon that gland, develop a toxic goiter subsequent to the pregnancy.

The problem then in preventing congenital goiter is assuring a sufficient amount of thyroxin to care for the needs of both mother and child. In women with normal thyroid glands, this can be done by maintaining an iodine intake sufficient to enable the thyroid gland to produce the necessary thyroxin. If the iodine in the food and water is deficient, more must be added. To the woman with a thyroid so deficient that it cannot produce the necessary amount of thyroxin, dessicated thyroid is given. Iodine should not be given to the woman with a non-toxic goiter of the adenomatous type, as it is liable to be made toxic thereby. Some time ago I conceived the idea of giving the patients of this group a small amount of dessicated thyroid. This has been done by my associate in the goiter clinic, Dr. C. E. Brous, and although his experience at the present time is too limited for a positive statement, we believe that this is going to be the solution of the prevention of congenital goiters in children of women with glands of the type which make it unsafe to give iodine.

The causes of goiter may be classified as primary and secondary. The primary causes of goiter are first, and chief, a deficiency in the iodine intake; second, anything that lowers the ability of the thyroid to utilize iodine; and third, anything that increases the thyroxin need above that which a partially deficient thyroid can produce. Iodine deficiency as a cause of goiter is an undisputable fact and is universally accepted by everyone who has made a really scientific study of the problem. The relationship of the existence of goiter and iodine deficiency in the great goiter belts, such as the Great Lakes Basin and on the Pacific Coast where the surface water, and hence, the vegetation, is deficient in iodine, cannot be doubted. The best proof of this statement occurs in northern Michigan, where there is one district in which practically everyone has an enlarged thyroid and in which the surface water is absolutely devoid of iodine.

The iodine intake in food and water may be sufficient, deficient, or relatively deficient. It is sufficient when there is a sufficient amount of iodine to meet the demand for thyroxin at any time and in any amount. It is deficient when there is not enough iodine to meet the need even under minimum activities. It is relatively deficient when there is a sufficient amount of iodine to produce the necessary amount of thyroxin under ordinary conditions but not enough to produce the necessary amount of thyroxin when there is an extra load demanding an increased amount of thyroxin. Examples of this are seen in individuals who, under ordinary conditions, have normal functioning thyroid glands, but who develop a goiter as a result of excessive physical or mental strain or disease.

The thyroid in its ability to utilize the iodine furnished to it must be classified as efficient, deficient, or relatively deficient. The efficient thyroid gland is able to utilize iodine and produce the necessary amount of

thyroxin under all conditions. The relatively deficient gland is the gland that under ordinary conditions is able to produce a sufficient amount of thyroxin, but when the demand comes for more thyroxin, it is not able to produce it even though there is a sufficient amount of iodine. The deficient thyroid gland is the gland that is not able to produce thyroxin enough under any circumstances even though there is plenty of iodine at all times. Both the deficient and the relatively deficient glands may be unstable either because of a congenital abnormality or acquired changes.

Glands that are relatively or absolutely deficient, or in which there is a relative or absolute deficiency in the amount of iodine intake because of the regenerative power of the gland, may develop any of the hyperplastic forms of goiter. If the congenital goiter in man, as that in experimental animals, is the result of a maternal thyroxin deficiency, we can trace back most of those goiters which have not been the result of an actual disease of the gland to a primary iodine deficiency in the maternal ancestor, and while there are other determining factors that have an influence in the development of goiter, they are, in reality, playing secondary rôles. The perfectly normal thyroid gland, which is receiving a sufficient amount of iodine, will not develop a goiter, but a perfectly normal thyroid gland receiving an insufficient amount of iodine or a thyroid gland with lowered efficiency produced by infection or toxins or other lesions so that it cannot utilize the iodine that it receives, usually results in the production of some form of goiter.

The prevention of goiter in the individual born with a normal thyroid gland is merely that of supplying a sufficient amount of iodine. We hear a great deal said about the danger of iodized salt, but the experience of using the iodides in syphilis in the days gone by has demonstrated conclusively that it does not carry any danger to the ordinary individual. The danger is only to the individual with the abnormal thyroid gland and it is my personal opinion that it occurs only in the thyroid which has undergone a hyperplasia so that there is a markedly increased number of cells which have been lying dormant and may be stimulated into activity by the giving of iodine over a long period of time.

A comparative study of the acini of the colloid goiter with that of the normal thyroid gland indicates the type of treatment required. The cells secrete two known substances; one, thyroxin, and the other, colloid. Colloid appears to be an inert substance filling the acini, its purpose being either that of holding the iodine in suspension until needed for the production of thyroxin or holding thyroxin in suspension until needed. I am personally inclined to believe that it is the former. When in the presence of an iodine deficiency, a demand is thrown upon the thyroid gland for more thyroxin, the cells set about trying to produce it. In this attempt, there is an over-secretion of colloid distending the acini. As the acini become distended with colloid, the margin is stretched, flattening the cells both by the stretching their bases and the increased intra-acinar pressure due to increase in colloid. In well marked cases, the cells become so flat-

tened that the protoplasm at the sides of the nuclei is not as thick as the nuclei. Such cells can not be expected to secrete normally.

A few years ago in the goiter clinic of the University of Oregon Medical School, we divided our patients with simple colloid goiter into four groups. One group was given ten milligrams of iodine daily, one group was given one grain of sodium iodide three times daily, another group was given larger amounts, and another group was given one grain of dessicated thyroid daily. The patients were seen every two weeks and the thyroid gland examined, the neck measured, the pulse counted, and other observations made as indicated. The length of the treatment varied from a few weeks to two years.

Later three of us independently went over the records and came to the same conclusion, viz.: iodine does not cure simple colloid goiter in a majority of cases, but dessicated thyroid does. In the iodine series, the results were practically the same regardless of the amount. A few were cured. The most of them were not. Some of the goiters on iodine decreased in size and then increased while iodine was being given. Experimentally, we have shown that the increase in colloid begins within two days after reducing the thyroid capacity by operation and that if there is not some relief, the hyperplasia begins within a week. That hyperplasia does not take place in all glands is, I believe, due to the fact that the added stimulation enables the thyroid to utilize the iodine to a better advantage. There is no organ in the body that is one hundred per cent efficient, and we have no right to believe that the thyroid gland is absolutely efficient. With an increased activity on the part of the cells, it may utilize the iodine to a greater degree of efficiency than it was doing before. This I think explains the reason for not getting the early hyperplasia in all colloid goiters.

The fact that the giving of iodine to patients with colloid goiter does not produce results in a majority of such patients is due to this deficiency of the cells. The treatment then is to put these cells at rest by supplying the thyroxin already prepared until the colloid can be absorbed and the cells come back to normal. It has been our custom in the goiter clinic of the University of Oregon to give patients with a simple colloid goiter one grain of dessicated thyroid three times a day. Occasionally some patients require more. It has been our general experience that patients with a simple colloid goiter are cured within a period of two or three months. So firmly are we convinced of the truth of this statement that to those patients in whom cure does not result in that period of time, we state that there has been error in the diagnosis. We have seen the patient too late when hyperplasia had already occurred. This we have proved by operating upon some of them who later became toxic and finding a diffuse adenomatous type of goiter.

In the treatment of toxic goiter, iodine in the form of Lugol's solution has been found invaluable in the preparation of the patient for operation, regardless of the type of goiter. It must be used, however,

with caution. It must not be used indiscriminately, as some patients are harmed by the prolonged use of Lugol's solution. It has been our experience that when this has occurred, these patients do not readily yield to Lugol's solution again.

So far I have dealt with the use of iodine in the preparation of the patient for operation. In reviewing the literature, we find frequent references to patients who have not been cured. Some time ago I made a study of the patients seen in the goiter clinic who have been operated upon without a complete cure. As a result of this, we were able to classify the patients of this group as follows: First, errors in diagnosis, that is, the symptoms the patient had were not due to a thyroid lesion; second, late operation, the patient having had permanent lesions produced previous to the operation. The operation had cured the goiter and there was no longer any hyperthyroidism, but the patient still had a damaged heart and nervous system and symptoms of goiter present because of these permanent lesions; third, incomplete operation, in which case the patients have never been cured; fourth, true recurrences.

To study the cause of true recurrences, we carried on experimental work on dogs and rabbits and found, first, that it was possible to remove a minimum amount of thyroid without producing any reaction in the thyroid gland at all. In other words, we left enough thyroid gland to produce the necessary amount of secretion so that there was no need for any compensatory change. Second, we found that when the maximum amount of the thyroid gland was removed, leaving only a very small portion, there were certain uniform changes that always occurred. These were first, an increase in the amount of colloid which appeared within two days, and second, a hyperplasia that began at the end of the week. Third, we found that when an amount between these extremes was removed, if the animals were given iodine there would be no reaction; but, if they were not given iodine, hyperplasia occurred. Our experimental animals could be classified in their relationship to thyroxin production as follows: first, thyroxin efficient, in which there was enough thyroxin produced to meet the animal's need; second, relatively deficient, in which, when iodine was not given, the hyperplasia took place because there was a thyroxin deficiency, but when iodine was given, hyperplasia did not take place because the cells were able, with an excess of iodine, to produce enough thyroxin; and third, thyroxin deficient, in which there was not enough thyroid tissue to produce the necessary amount of thyroxin even though the gland was kept saturated with iodine. In this group, hyperplasia always took place.

We next studied the influence of iodine upon the hyperplasia. There had appeared in the literature a discussion between Loeb and Marine as to the effect of iodine upon hyperplasia. We found that when the gland was kept saturated with iodine by giving Lugol's solution, the hyperplasia continued usually up to about the end of the third week, occasionally a few days longer, there being two exceptions in which it was not completed

within a month. We found, further, that when iodine was not given, the hyperplasia was much more extensive and in two instances it produced an actual goiter in dogs that had a normal thyroid gland before operation. In no instance did we see a goiter develop in a dog that received a sufficient amount of iodine during the period of regeneration.

We then applied this to our patients. The patients all have the thyroid gland saturated with iodine previous to the operation by giving Lugol's solution in 10 to 25 minim doses, three to four times daily, according to the severity of the goiter. Following the operation, we give Lugol's solution in 15 to 30 minim doses by rectum the first two days, three or four times a day. After this, we give 10 minims by mouth three times daily for the first month following the operation, and then 10 minims once a day for the next month, and then follow up with iodized salt or iodine tablets. Since we have followed this regime, we have seen just one patient who has returned with a toxic goiter, due to excessive regeneration. This occurred in a foreigner who could not understand English well and had neglected to take the Lugol's solution as directed.

#### SUMMARY.

We may sum up our present knowledge of the relationship of iodine to the thyroid gland as follows:

1. Iodine constitutes a high percentage of the thyroxin molecule and is therefore essential to its secretion.
2. Goiter develops as the result of the continued iodine deficiency in the diet.
3. Congenital goiter occurs in the presence of a thyroxin deficiency in the mother and can be prevented by maintaining a sufficient iodine intake for the mother with a normal thyroid gland and giving dessicated thyroid to the mother with a deficient thyroid.
4. Goiter can be prevented in those born with a normal thyroid gland by maintaining sufficient iodine intake unless the efficiency of the thyroid is later lowered by disease.
5. Iodine relieves hyperthyroidism but does not cure in the majority of cases and should be used only for preparing patients for operation.
6. The thyroid gland should be kept saturated with iodine following subtotal thyroidectomy in order to prevent excessive regeneration.
7. Following regeneration a sufficient iodine intake must be maintained in order to prevent recurrence.

# A STUDY OF THE STIMULATING EFFECT OF THE TESTICULAR SUBSTANCE ON SUGAR METABOLISM

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There are reported in the literature contradictory results on the effect of castration on metabolism. Loewy and Richter (1), for example, found that the removal of the ovaries decreased oxygen consumption and that the administration of dried ovaries to these castrates increased it, while Lüthje (2) on the contrary found that castration in dogs of both sexes had no influence on metabolism. Mitchell finds that castration of cockerels lowers their basal metabolism (3).

It is recognized that castration produces a profound change in the activity of an animal. A very active, unruly and pugnacious animal, such as a bull or stallion for example, becomes very subdued and easily managed after castration. Hoskins (4) found that castration greatly decreased voluntary activity and that testicle grafts failed to bring about any significant improvement in activity. Increased activity is always accompanied by an increase in metabolism, and since the animal derives most of its energy from the metabolism or oxidation of sugar, it was thought desirable to study the effect of the testicular substance on sugar metabolism.

The respiratory quotient is the index usually used to the amount of sugar metabolized, a rise in the quotient indicating an increase in sugar metabolism, and a fall a decrease. In this investigation, sugar utilization, as well as the effect of the testicular substance on its utilization, was determined directly according to the following procedure.

Seven hundred cc. of 0.1 per cent dextrose solution was prepared and divided into portions of 100 cc. These 100 cc. portions were introduced into beakers. Twenty mgm. of the testicular substance\* were introduced into one beaker, and 40, 60, 80 and 100 mgm. into other beakers. Two gold fish of approximately the same size and with a combined weight of approximately 5 gm. were then introduced into the beakers. Air was bubbled through the sugar solutions to insure an adequate supply of oxygen to the fish. The two beakers containing gold fish and sugar solutions to which nothing was added served for controls. Sugar determinations were made according to the method of Benedict immediately and after 30 hours. The averages for 4 series of experiments are shown in Figure 1, under "testicular substance." It will be seen that the average amount of sugar used in 30 hours by the controls was 22 per cent and that the fish in the

\*The testicular substance used in this investigation was a Parke, Davis & Co. preparation. It is sold under the name of "Orchic Substance" and one grain of the powder represents 10 grains of the fresh gland.



sugar solutions to which 20, 40, 60, 80 and 100 mgm. of testicular substance were added used 54, 67, 74, 77 and 78 per cent of the sugar respectively. By comparing these figures it will be seen that the testicular substance increased sugar utilization and the greater amount of the substance used, the greater the increase produced.

One of us had already shown that the ovarian substance increased sugar utilization in the unicellular animal, *Paramecium*. The object of repeating this work and reporting it in this paper was to determine, in the first place, if the ovarian substance would increase sugar utilization in a higher animal, such as the gold fish, just as it was found to do in

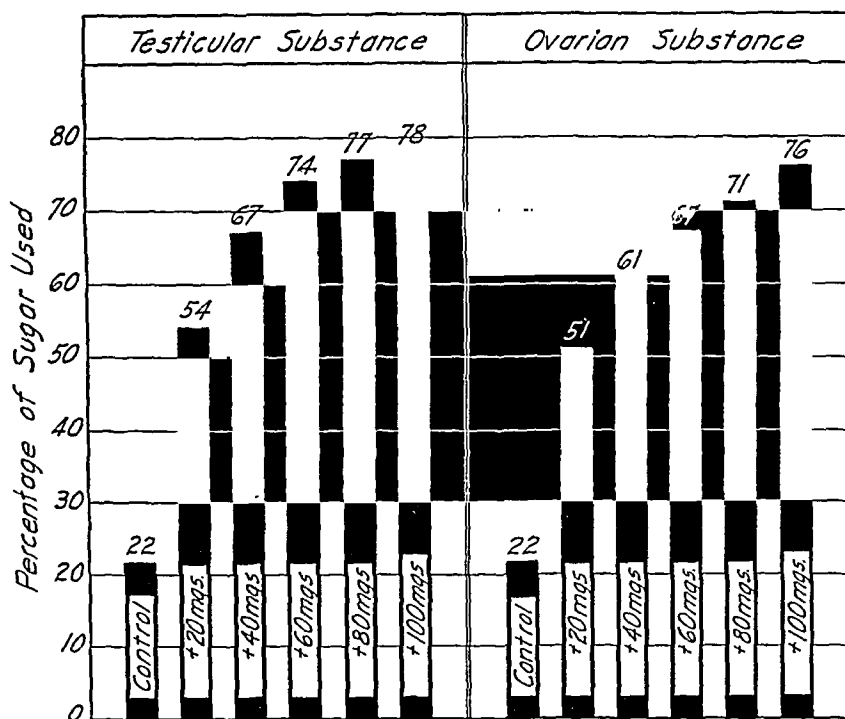


Fig. 1. Chart showing the stimulating effect of varying amounts of the testicular and ovarian substances on sugar metabolism.

the unicellular animal, and in the second place, to compare the effect of the ovarian substance with that of the testicular substance, using the same kind of animal.

The method of procedure with the experiments with the ovarian substance\* was identical with that used with the testicular substance. As a matter of fact the experiments were made at the same time and under identical conditions, and for that reason, as may be seen in Figure 1, the controls used exactly that same amount of sugar, for the controls were the same in both series of experiments.

It will be seen in Figure 1, under "ovarian substance," that the fish to which 20 mgm. of ovarian substance were added used 51 per cent of

\*The ovarian substance used in this investigation was a Parke, Davis & Co. preparation. It is sold under the name of "Ovarian Substance" and one grain of the powder represents six grains of the fresh gland.

the sugar against a control of 22 per cent, and the fish to which 40, 60, 80 and 100 mgm, were added used 61, 67, 71 and 76 per cent of the sugar respectively. By comparing these figures, it may be seen that the ovarian substance increased sugar utilization just as did the testicular substance.

The following precautions were taken and checks made in the preceding experiments. Air was bubbled through sugar solutions for 30 hours without the presence of fish and it was found that this had practically no effect on the sugar solution. Air was also bubbled for 30 hours through sugar solutions into which had been introduced the testicular and ovarian substances without any effect on the amounts of sugar in the solutions. It was found that the sugar was used only when the fish were present and the utilization ceased upon the removal of the fish. From these observations it was concluded that the fish were responsible for the utilization of the sugar observed in these experiments and not bacteria or yeast.

#### SUMMARY

1. The effect of various amounts of testicular substance on the rate of sugar metabolism of gold fish was studied. It was found that this substance stimulated sugar metabolism, the greater the amount used, the greater being the stimulating effect.

2. Ovarian substance also stimulated sugar metabolism of the gold fish, as it had been found to do in the unicellular organism, *Paramecium*.

3. It is concluded that both the testicular and ovarian substances would be found to have the same effect on the higher animals and man if the effect in these instances could be tested out directly as was done in the experiments reported in this paper.

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# THE STRUCTURAL CHANGES WHICH TAKE PLACE IN THE THYROID GLANDS OF GUINEA PIGS DURING THE PROCESS OF COMPENSATORY HYPERTROPHY UNDER THE INFLUENCE OF IODINE ADMINISTRATION

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In two previous publications (1) we have studied the effect of iodine administration on compensatory hypertrophy of the thyroid gland in guinea pigs; in a more recent, not yet published, series, we have extended these observations. In this paper we wish to correlate the facts thus established concerning the effect of iodine on the growth processes taking place in the thyroid gland with structural changes associated with these growth processes. In addition we shall refer more briefly to more recent experimental studies of Gray and Loeb (2) and of Rabinovitch (3) from our laboratory in which a marked effect of the administration of potassium iodide on the mitotic proliferation in the normal thyroid gland of the guinea pig was established. Furthermore, we wish to point out some of the problems still to be solved and to suggest some way in which previous observations concerning the effect of iodine on the thyroid gland might perhaps be harmonized with results obtained by Gray and Loeb, and by Rabinovitch.

We shall compare the conditions found in animals to which KI has not been administered (controls) with those observed in guinea pigs which have been under the influence of KI (iodized animals).

1. *A comparison of the growth processes in general in these two groups of animals shows that administration of KI does not prevent compensatory hypertrophy, but on the contrary makes it, on the whole, more pronounced. The number of animals showing hypertrophy was greater in the iodized animals and, furthermore, the average intensity of this process was also greater in the latter. However, in making these comparisons we must take into consideration the fact that, as a result of the stimulation caused by KI in the thyroids of these guinea pigs, secondary changes take place in the course of time which tend to obscure the hypertrophy. In the iodized guinea pigs definite changes occur in the character of the colloid, which cause an increase in the contents of the acini and thus lead secondarily to an increase in the pressure exerted on the whole wall and above all on the epithelial lining of the acini. Furthermore, the growth of the thyroid during compensatory hypertrophy does not take place through apposition of new acini in the periphery of the gland, but it con-*

sists in an increase in the number and size mainly of the epithelial cells of the acini, although an occasional mitosis may also be seen in the stroma, in particular in the vascular endothelium. Thus, as a result of the growth itself, the pressure within the gland remnant must be increased and must lead to conditions which are injurious, if the surrounding tissue opposes the necessary expansion of the gland. However, at no time do we see degenerative changes taking place in the thyroid gland which could be interpreted as caused by the iodine administration as such. Where no pressure is exerted on the gland cells they appear normal; in general neither cytoplasmic nor nuclear degenerations are noticeable. But even where pressure may secondarily obscure the hypertrophy of the gland, we can always find indications that these secondary changes affected cells which had previously been hypertrophic; however, very often we observe in the iodized guinea pigs a marked increase in the size and mitotic proliferation of the acinus cells and also an increased prominence of granules, in that part of the hypertrophic cell which adjoins the colloid. Occasionally we see, in such acini, multiple elevations consisting of hypertrophied epithelium protruding into the colloid. It is probable that these blunt papillae are due to growth processes taking place under conditions which do not permit a free expansion, although we must consider also the possibility that similar prominences may develop as a result of perforations in the wall separating adjoining acini. In rare cases, the epithelium, instead of protruding into the lumen of the acini in the form of papillae, may push, in an outward direction, into the underlying stroma.

2. *Modifications in the character of the colloid during the process of compensatory hypertrophy in controls and in iodized guinea pigs.* The characteristic change which takes place in the colloid during compensatory hypertrophy consists in softening and in solution processes. While it occurs in both controls and iodized animals, it is much more pronounced in the latter. Inasmuch as during the liquefaction the colloid takes up water and thus acquires a greater volume, certain consequences may result. It is possible that not only liquefaction but also an increased new formation of very soft colloid takes place. In some acini very soon the more or less liquefied colloid, which stains only very slightly or not at all with eosin, in contrast with the hard colloid of resting glands, which stains intensely with eosin, is absorbed, whereas in others it is retained, thus exerting pressure on the walls, especially on the epithelial lining of the latter, and causing a distension of the acini. In other instances, in which the absorption has progressed very far, the cavity of the acini becomes transformed into slits, lined by hypertrophic, high epithelial cells, in which the granular character of the cytoplasm is very distinct. Where the liquefied colloid has largely been retained, a gradual flattening of the epithelium, as well as a thinning of the walls, takes place as a result of the pressure. We can now find all transitions from the original hypertrophic epithelium to the epithelium flattened by pressure; if the latter

changes have become very pronounced, it may be difficult to recognize that this condition developed from a preceding state of hypertrophy.

If only a softening of the colloid has taken place without an actual liquefaction, we find this substance still taking the eosin stain, but less intensely than in the normal, less active gland. Because of its softness, the colloid is sticky and it adheres to the epithelial lining of the acini with threads, between which are found vacuoles of different sizes. This peripheral layer of vacuoles is quite characteristic of this type of colloid. Whether the formation of these vacuoles is due to solution processes in the peripheral colloid, which take place under the influence of the adjoining epithelial cells, or whether they are due to a retraction of the colloid caused by dehydration, which occurs during the process of fixation and embedding of the tissue, or whether it is due to both these processes combined, cannot be decided definitely at the present time. This condition is related to that observed in the normal gland, where in general the hard colloid is slightly retracted from the epithelial lining, evidently as the result of the shrinking taking place during the embedding of the tissue; but owing to the hardness of the colloid, the retraction in this case is very slight, whereas in the more watery colloid, which develops during compensatory hypertrophy, the retraction is much greater. Between these various states we find all degrees of transition and we can also observe different stages in the process of softening and solution of the colloid. Thus we not rarely find in the cavity of an acinus a more solid plate of colloid in the center, surrounded by a peripheral pale zone, in which the solution of the colloid has advanced much farther. We would interpret this condition as indicating that the liquefaction process proceeds in the direction from the outside towards the center. In other cases the outlines of the colloid have a ragged appearance, as though eaten out by some dissolving agent; or in still other cases we may see a pale plate of colloid, surrounded by an entirely liquefied zone. Occasionally we note in a disc of pale, soft colloid a number of red round spots, which represent either particles of colloid, that have resisted the solution processes longer than others, or which represent the remnants of phagocytes, which have undergone degenerative processes and which thus have become converted into balls not unlike colloid. It seems that phagocytes in the colloid may undergo such a type of degeneration. All these changes we may observe, although with unequal frequency, in the controls as well as in the iodized animals.

There is reason for assuming that these softening and solution processes are caused by a substance, presumably of an enzymatic character, which is given off by the epithelial cells when they are in a state of stimulation, such as we find during the process of hypertrophy, and perhaps the prominence of granules in that portion of the cells directed towards the lumen of the acinus indicates the preparation of enzymatic substances on the part of the epithelium. These solution processes, although occur-

ring also in the controls, are proceeding on the whole with much greater intensity in the iodized animals.

However, there exists a second mode by which the colloid can be dissolved, namely, through the action of phagocytes; the latter succeed in dissolving the colloid locally, either directly, or they may first take little particles of colloid into their cell body and thus destroy it; which of these two processes prevails is difficult to decide. Subsequently these phagocytes degenerate, either by karyorrhexis or by karyolysis, and thus leave cavities in the colloid at the point where they have been. The cavities developing in this manner are usually of the size of the average phagocytes, but occasionally they may be larger, probably owing to a swelling which these cells undergo during the process of degeneration. Thus isolated or multiple holes may develop in the colloid and often a honeycombed appearance may be produced; in extreme cases only a few shreds of colloid may remain. However, these phagocytic cells succeed in causing such a localized solution of the colloid only in case the latter substance has already previously been softened to a considerable extent; they are unable to dissolve the hard colloid usually found in the normal non-stimulated gland, especially in the peripherally situated acini. Also this phagocytic activity is much more pronounced in the iodized animals during the process of compensatory hypertrophy than in the controls; and the same difference between the phagocytic activity in these two classes of guinea pigs we find also in the intact thyroids of animals which have not previously been submitted to a partial extirpation of this gland, as Gray and Loeb, as well as Rabinovitch, have shown.

There is still a third way in which a solution of the colloid can take place, namely, through the activity of the polymorphonuclear leucocytes. We have observed this condition in only one case in a control animal, in which evidently some infection had taken place, although the guinea pig had gained in weight during the course of the experiment. In this case the whole gland presented a honeycombed appearance; thin and compressed walls separated large, irregularly shaped acini, filled with very pale and partly dissolved colloid or with colloid which had still a slightly greater consistency and which therefore took on a light pinkish color and was much retracted, changes which indicated that certain solution processes had taken place. In some of the large acini these solution processes in the colloid had gone so far that frequently only shreds of colloid were left. While the epithelial cells were often somewhat vacuolar, they were still enlarged, owing to compensatory hypertrophy which had taken place, and they showed frequent mitoses, notwithstanding the pressure exerted upon the walls of the acini. As the result of this pressure, the latter were in various places in process of perforation and in the end only remnants of them in the form of spurs were visible. In the lumen, as well as in the walls of many acini and in the tissue surrounding the gland, there were numerous polymorphonuclear leucocytes, which were largely responsible for the marked solution processes occurring in the colloid, the intensity

of solution in a definite location corresponding to the number of leucocytes present. Also in the vessels of the tissue surrounding the thyroid remnant there were many leucocytes, whereas in the perivascular areas we observed masses of lymphocytes together with an admixture of polymorphonuclear leucocytes. In addition some mononuclear phagocytes were found in the remaining parts of the colloid.

We may mention here that there exists still another condition in which solution of the colloid takes place, namely, in autolysis; for instance, in thyroid tissue kept *in vitro* under unfavorable circumstances we observe a marked liquefaction of this substance.

We see then that in principle the same solution processes occur in the thyroids of iodized as well as in the control guinea pigs, but they are more pronounced in the former; also the absorption of the liquefied or partly liquefied colloid is here less rapid, and thus in the iodized guinea pigs this material collects to a larger extent in the acini and distends them. However, there is only a quantitative difference existing between these two sets of guinea pigs, as in both an accumulation as well as an absorption of the liquefied colloid occurs, but in different degrees.

Furthermore, we see not only differences in different individuals in the degree of hypertrophy of the cells and in the intensity of solution processes in the colloid of the gland remnants, but even in different parts of the same gland. Thus in both controls and iodized guinea pigs there is, on the whole, a greater tendency on the part of the colloid to remain solid in the most peripheral acini. This is associated with a lowered activity of the epithelium, which is flatter here, whereas in the center the colloid is on the average softer and the hypertrophy of the epithelium is more pronounced. There is perhaps also, in the iodized animals, a greater tendency towards the absorption of the softened and liquefied colloid in the central acini and to its retention in the peripheral acini. We suggest that these differences between the central and peripheral acini are not, as has been maintained, due to differences in the embryonal origin of these gland constituents, but to differences in the vascularization and perhaps also to differences in pressure effects, which exist between the peripheral and central areas of the thyroid. The central portions of the gland seem to be under more favorable conditions in this respect than the peripheral parts. However, hypertrophic processes occur also in the peripheral acini and may be especially prominent in the iodized guinea pigs.

In describing the conditions observed in the colloid we may briefly refer to two minor changes which may here occur. Not rarely we observe the remnants of hemorrhages in some of the acini; in such cases the extravasated blood may either form a dense disc or ball in the center of the colloid or in some cases it may lie crescent-like on the periphery of this substance. It is probable that these hemorrhages are due to trauma inflicted upon the thyroid at the time of the operation, when parts of the gland tissue were extirpated. Furthermore, trauma, in particular pressure exerted on certain peripheral parts of the gland remnants, may cause a

pushing of cell masses into the colloid, which thus in some areas may almost entirely fill the cavities of such acini.

3. *Pressure effects in the gland remnants of the control and of the iodized guinea pigs.* As we have mentioned, there are two factors which may lead to pressure effects in the thyroid gland, namely, (1) growth processes of a non-appositional character, taking place in the gland and associated with the usual production of colloid; (2) changes taking place in the colloid and consisting in the production of a large amount of solid material, which, instead of being absorbed, remains in the lumen of acini. This condition is found especially in the peripheral acini in normal glands, where the colloid is hard and present in a relatively large quantity; but even in hypertrophic gland remnants there is still a tendency for the colloid in the peripheral acini to be harder than in the central areas. There is a third factor which may lead to pressure, namely, a very rapid and intensive liquefaction of the colloid due to the taking up of water, which causes an increase in volume of the contents of the acini, a liquefaction which may or may not be associated with an increased production of colloid. We find this condition in certain acini in compensatory hypertrophy of thyroid remnants, but it becomes much more prominent if animals during the process of compensatory hypertrophy are fed or injected with KI. Also in otherwise normal guinea pigs, in which the thyroid gland has been left intact, Gray and Loeb, as well as Rabinovitch, observed in the later periods of KI administration a tendency on the part of the colloid to liquefy. In the iodized animals with compensatory hypertrophy,—and a similar condition we find in animals in which the thyroid has been left intact in the late stages of iodine administration,—the liquefied colloid has in general less tendency to be absorbed than in controls, which are in the process of compensatory hypertrophy, and thus this substance, accumulating in the gland, necessarily exerts pressure on the walls separating adjoining acini. This pressure will make itself felt more in the center of the wall than near the corner points where neighboring acini adjoin each other. It leads first to a flattening out of the epithelium which affects more or less the whole lining of the acinus; but it acts also on the stroma and in particular on the capillaries in the wall, which latter, on the one hand, supply the tissues with necessary substances, and, on the other hand, serve as an instrument through which absorption of the contents of the acini takes place. Both these processes must therefore be interfered with, if the pressure becomes strong enough. The pressure on the epithelium also has certain consequences. The mitotic proliferation in the epithelium decreases and, when the flattening out of the epithelial layer has become very pronounced, it ceases altogether. Furthermore, we may assume that the pressure and consecutive flattening of the wall will also interfere with the production and secretion of colloid and presumably also, in the end, with the production and secretion of the enzymes which, as we may suppose, are responsible for the diffuse solution which takes place in the colloid in cases of compensatory hypertrophy and which is



so much increased in iodized guinea pigs. At last the wall separating two adjoining acini may become in places a thin flat band and it may break through in the center. It is only in exceptional instances that we see the epithelium, at a point where the pressure is greatest, become necrotic preceding the perforation; no sign of degeneration outside the pressure effects is noticed in the thyroid acini under usual conditions. As a result of these perforations adjoining acini are thus united. At first, spurs, representing the remnants of the wall, still project into the lumen and indicate the place where the perforation has taken place. Then the contents of the acini unite and the spurs may become gradually shorter and in the end may disappear; thus two or even a larger number of medium-sized acini may have joined in the formation of one very large acinus, in which all indications of such an origin have disappeared. It appears probable that when such changes have taken place in acini in which the colloid has become liquid, the latter may be gradually absorbed, if the epithelium, now forming the walls of the larger, new acinus, functions again and then a secondary decrease in size in such acini may take place owing to the pressure exerted by the surrounding tissue. Thus we may explain an apparent incongruity in certain cases between the relatively small increase in size of the whole thyroid or of the thyroid remnant and the considerable mitotic cell proliferation which has taken place under these conditions. Similar perforations are found in peripheral acini of normal glands when, as we have seen, the large amount of solid colloid exerts a certain pressure, and thus even here a constant transformation in structure occurs, but perforations seem to be much more frequent, as far as we can judge without having actually made comparative counts, in glands which are in the process of compensatory hypertrophy and especially in animals receiving at the same time iodine. During compensatory hypertrophy they are seen not only in the peripheral parts of the gland, but also in the central areas; and in such structures we have to deal not only with narrow thin spurs projecting into the lumen of the acini but also with papillae lined with hypertrophic cells. The latter kind of projections may owe their origin to perforations which took place in walls in which the epithelium either had already undergone compensatory hypertrophy at the time of perforation or which underwent hypertrophy subsequent to the time of perforation. We find all transitions from this condition to that in which the wall of an acinus is lined by hypertrophic epithelium, projecting into the lumen of the latter in the form of multiple short and blunt papillae. The origin of such multiple projections is not certain. They may be due to growth processes during which the proliferating epithelium is forced to fold and to protrude into the lumen of the acinus, or they may represent the remnants of multiple perforations, in which a number of adjoining acini are at last united into a single acinus.

There still remains to be explained the fact that, in so many acini in which liquefaction of the colloid takes place in iodized guinea pigs during the process of compensatory hypertrophy, the more or less fluid

material is not absorbed, but remains in this condition and causes distension. However, as we have seen, this is not always the case in iodized guinea pigs; even in these a considerable absorption of this fluid may take place similar to that usually seen in controls during the process of compensatory hypertrophy; conversely also in the latter a retention of fluid may occur. But a quantitative difference exists in this respect between these two classes of animals, and two factors are perhaps responsible for the lack of absorption in the iodized guinea pigs. In the first place there may be so great a rapidity in the solution process in the colloid that it leads to early pressure effects, which interfere with the absorption of fluid. Associated with this process there may perhaps be also a more active new formation of fluid colloid. In the second place, there may be, as a result of the stimulation by iodine, so much hormone carried into the circulation that a saturation occurs and thus mechanisms are set in motion which inhibit this excess elimination of colloid into the circulation. However, it is not probable that after extirpation of so large a part of the gland the organism as a whole is supplied with such an excess of hormone. Furthermore, the localized appearance of this retention in the gland renders it more probable that we have to deal with local factors like pressure rather than with general effects or the whole organism and with regulations following these effects. Moreover, in the peripheral acini of normal glands, the retention of colloid and consecutive pressure effects, which, we observe, must be explained as due to localized conditions. On the other hand, the retention of softened or liquefied colloid in the whole glands of iodized guinea pigs, which is found especially in later stages of iodine administration, is probably due to an over-activity of the gland, taking place under the stimulus of iodine, not accompanied by a sufficient discharge of this material and therefore followed by pressure effects. We must consider the possibility that a regulatory mechanism diminishing the absorption of colloid may play a part in the latter kind of cases.

4. *On the character of the phagocytes found in the colloid of control and iodized guinea pigs.* In discussing the solution processes in the colloid, we have referred already to the activity of phagocytes, which cause a localized softening and solution of the colloid and which later degenerate. These phagocytes appear in especially large numbers in the iodized animals, although they may be numerous also in the controls. They are found preferably in acini in which the colloid is softened and has therefore become somewhat paler. They are not usually found in acini in which the colloid is completely liquefied or has become absorbed. In case the colloid is still hard, there are either no phagocytes present or they are small or merely the nuclei remain visible. This condition is observed in control as well as in iodized animals; also in the former the phagocytes are more numerous and larger, in places where the colloid is pale and soft. The phagocytes in the controls are therefore on the whole more frequent in gland remnants, which show a higher degree of hypertrophy, probably because the softening of the colloid follows a course parallel with the

degree of hypertrophy. However, it is possible that in addition to the action of a mechanical factor certain metabolic processes in the acinus epithelium, or in the colloid adjoining the epithelium, may attract the phagocytes.

In hard colloid the phagocytes cannot produce solution processes, but here they seem gradually to degenerate and disappear; perhaps also the separation of solid balls out of the colloid may be due to the activity of these cells. In soft colloid phagocytes take up particles of this material and dissolve it; they may then swell and after degeneration leave holes in the colloid which are very large.

The phagocytes may take up also isolated red corpuscles which have entered the colloid, or occasionally they may enclose even desquamated epithelial cells. In rare cases mitoses or the presence of two nuclei can be observed in such phagocytes.

While, as stated above, degeneration usually leads to solution of the phagocytes, following karyorrhexis or karyolysis, it seems that some of these cells may become transformed into round bodies, staining intensely with eosin and thus, in the end, resembling solid colloid material, which is perhaps identical with the solid balls in the colloid to which we have just referred. In addition we occasionally observe, in the colloid, cells with dense eosinophilic cytoplasm and a central round intensely staining nucleus; these cells are similar to those which may occasionally be seen in the epithelial lining of the acinus. They also represent, probably, an early stage of degeneration.

As to the origin of the phagocytic cells, certain observations which we made may be of interest. In certain cases, in iodized as well as in control animals, we noticed connective tissue breaking through the wall of the acinus into the colloid. Here some cells, situated in the connective tissue, rounded off, detached themselves from the rest and became phagocytes. It seems, then, that certain stroma cells may undergo this transformation. On the other hand, we also observed that, as a result of growth processes in the epithelial lining of the acini, the epithelial cells were pushed in the direction towards the cavity of the acinus; they then desquamated, finding there less favorable conditions in the supply of oxygen and food stuffs. In view of the fact that epithelial cells lining the acinus may take up particles of red corpuscles or of pigment derived from the latter, it is not improbable that also the desquamated epithelial cells may act as phagocytes. In addition we must consider the possibility that lymphocytes, which seem to be increased in the stroma of iodized guinea pigs, may migrate into the colloid, increase here in size and thus become converted into phagocytes.

5. *Structural variegation as a characteristic of the thyroid remnants in iodized animals.* We have seen that certain structural characteristics are usually associated in the acini of the thyroid gland. Thus, almost complete liquefaction of the colloid is, as a rule, associated with distension

and enlargement of the acinus, while at the same time a gradual flattening of the hypertrophied epithelium through pressure occurs and ultimately perforation and spur formation. The colloid does not take the eosin stain well and appears, therefore, pale. Medium-sized acini may be associated with pinkish colloid, containing a peripheral zone of vacuoles, and with a markedly hypertrophic epithelium. Fargoning absorption of the softened colloid is, in certain cases, observed in acini in which the lumen has been reduced to the form of irregular slits; in these the epithelium shows marked hypertrophy and the cytoplasm of the latter is distinctly granular. Solid, slightly retracted colloid is found in medium-sized or small acini with low or medium-sized, not hypertrophic, epithelium. However, in the peripheral zone of the thyroid, the acini, in which we find this type of colloid and epithelium, may be large, as a result of a preceding pressure perforation and union of neighboring acini. In addition, between these types of acini various transitions may be observed; furthermore, in the same gland remnant the appearance may be somewhat different in different parts. However, whereas in the control animals this latter condition is not very prominent, it is characteristic of the gland remnants of iodized guinea pigs. Here we often find, within the same gland remnant, areas with large acini and almost liquefied colloid, alternating with somewhat smaller acini, with partly absorbed and faintly pink staining colloid, or with pink staining, vacuolar colloid; in some cases we may observe in the center the appearance of slits. It is this variegated appearance in the iodized animals, and especially the presence of foci containing large acini with pale, largely dissolved colloid, which is characteristic of the gland remnants of the iodized guinea pigs. In the control animals the structure is usually much more homogeneous, the large majority of the acini, in many cases, showing somewhat hypertrophic epithelium and slightly softened pink-staining colloid in medium-sized or slightly enlarged acini. However, in both iodized and control animals areas may appear in which the colloid is hard and hypertrophy of the epithelium is lacking; but, as stated by us previously, in our experience such areas are more common and on the average more extensive in control animals. Thus this variegated appearance makes it possible in many, although not in all cases, to distinguish the thyroid remnants of iodized from those of control animals. It follows from what we stated above that the differences between these two classes of animals are not absolute, but only relative and of a quantitative character.

#### DISCUSSION AND CONCLUSIONS

We may consider it as proven that in the guinea pig potassium iodide, either given by mouth or injected interperitoneally, does not prevent compensatory hypertrophy. On the contrary, the number of cases in which compensatory hypertrophy is lacking is, in our experience, on the whole greater in the controls than in the iodized animals. This conclusion holds good irrespective of the size of the thyroid gland tissue which we leave

behind at the time of operation, within the limits tested by us. It holds good if we leave as much as one half of one lobe; also within the ranges of daily doses of 0.01 and 0.05 grams KI. Even with a daily dose of 0.1 gm. which would correspond approximately to so large an amount as 12-15 grams of KI in an adult man, the hypertrophy was not necessarily prevented, although it was, on the whole, diminished. As to the cause of the diminished hypertrophy in this latter case several factors have to be considered. In the first place the guinea pigs receiving so large a dose of iodine showed a relative loss of weight or at least a considerably smaller gain than the animals receiving a smaller dose. Now, we have observed previously that gain in weight during the course of the experiment favors the development of compensatory hypertrophy, whereas its absence, or even a loss in weight diminishes considerably the chances of compensatory hypertrophy. The unfavorable weight balance of the group receiving 0.1 gram KI daily, which was noticeable in our cases, may, therefore, at least partly explain the relative diminution in hypertrophy observed. The actual or relative loss in weight in this group may be accidental or it may be due to otherwise injurious effects of so large a dose of iodine; it is, however, also possible that, at an early period in the administration of such an amount of this substance, a pronounced functional stimulation of the gland takes place, leading to the production of an excess of thyroxin, which counteracts the stimulating effect of the iodine, and which thus would tend to induce a return of the thyroid to a resting state. While we cannot exclude this possibility,—and at later stages even in animals receiving the smaller doses of KI—still we can be certain that it is above all the pressure exerted on the walls of the acini by the increase in their content, in particular by the swelling and liquefaction of the colloid, which causes the flattening out of the epithelium and ultimately the perforation of the walls separating adjoining acini.

It is also this same factor which plays a part in reducing, in the course of time, the extraordinary increase in proliferative activity which takes place in the normal thyroid gland of guinea pigs, under the influence of administration of KI (Gray and Loeb, Rabinovitch); but in this case we have again to consider at least the possibility that ultimately an excess of thyroxin is produced, as a result of the increase in iodine intake, and that thus a tendency to the reduction in thyroid activity may follow at a later stage.

As to the marked increase in the content of the acini, it is essentially due to the taking up of water by the colloid and its subsequent softening and liquefaction. This process occurs in the controls as well as in the iodized animals, but with a much greater intensity in the latter, and thus there may result, in this group of animals, an early development of pressure, acting on the walls of certain acini, and an interference with the rapid absorption of the fluid which has accumulated in the acini. However, as we stated above, there exists in this respect only a quantitative difference between the controls and the iodized guinea pigs; in both groups

absorption as well as retention occurs, and in iodized as well as in normal glands the retention is, on the whole, more marked in the peripheral acini, where apparently the *circulatory conditions* are less favorable.

Another factor which may also play a rôle in diminishing absorption is perhaps an excess of thyroxin in the organism. Such an excess might result from its increased production following the administration of iodine. Our experiments, showing that compensatory hypertrophy is prevented by administration of thyroxin to a guinea pig, prove that it is the amount of active hormone present in the whole organism which here determines the productivity of the gland. In addition there may be a mechanism which regulates the rapidity with which thyroxin is given off by the thyroid gland and which may act in accordance with the needs of the whole organism. Uhlenhuth, especially, has emphasized the necessity of postulating a mechanism regulating the discharge of colloid as distinct from that regulating its production(4). It is not very probable, however, that an excess of thyroxin, as a limiting cause for the discharge of the colloid from the acini, would come into play after extirpation of the greater part of the thyroid gland, which in itself reduces the amount of hormone produced, but it might conceivably do so in normal guinea pigs which receive iodine, particularly at a time when softening of the colloid becomes noticeable. Furthermore, it is possible that this increase of content in the acini in both classes of iodized guinea pigs, those in process of compensatory hypertrophy as well as those in which the gland has remained intact, is not only due to an increased retention of colloid, but also to an increased production of colloid, which takes place under the influence of iodine administration.

The liquefaction of the colloid, which is thus so markedly intensified through the administration of iodine, is characteristic of a stimulated condition of the thyroid gland in general, except when special factors like infection or autolysis play a part. This softening and liquefaction is presumably due to an agent given off by the epithelial cells of the thyroid; it therefore presupposes an increased epithelial activity and the latter would be called forth by a stimulus developing as the result of the lack of thyroxin in the organism. Corresponding to this stimulated functional condition are the structural changes which we have described, namely, an increase in size of the epithelium and an increase in number and size of the cell granules in compensatory hypertrophy, with and without feeding of iodine. As we have seen, the latter substance increases the number of cases in which compensatory hypertrophy occurs, until such a time as secondary effects, in particular the pressure exerted by the excess of material in the acinus, produce injuries in the epithelium. The increase in the number of phagocytes in the thyroid of iodized guinea pigs is also indicative of a condition of stimulation.

There is an apparent discrepancy between the effects of iodine administration in the guinea pig—as observed by ourselves in compensatory hypertrophy and by Gray and Loeb as well as by Rabinovitch under normal

conditions—and in the dog, where Des Lignéris (5) and subsequently Marine (6) observed a filling of the acini with solid colloid. In human beings also, to judge from recent investigations concerning the effect of iodine in cases of Graves' disease, a solidification of the colloid may follow the administration of this substance. Perhaps the difference is more apparent than real. We may consider the possibility that in both cases iodine stimulates the thyroid gland; but whereas in the dog, and, under certain conditions also in man, such a stimulation leads to an over-production of colloid, which may exert pressure on the acinus wall and thus secondarily and at least temporarily reduce the activity of the gland; in the guinea pig this stimulation apparently leads to the increased preparation of a substance, perhaps of an enzymatic nature, which tends to liquefy the colloid.

As to the comparative number of mitoses in cases of compensatory hypertrophy in normal and in iodized guinea pigs, we have not yet made exact counts and can not, therefore, make definite statements; we know, however, that compensatory hypertrophy as such produces increased proliferative activity in the thyroid gland. Furthermore, if we compare sets of gland remnants in control and in iodized animals, the number of mitoses seems on the whole to be greater in the latter, because here the hypertrophy is more marked, if we compare all the experiments in both sets of guinea pigs. On the other hand, we have also observed that the increased pressure exerted by the liquefying colloid on the wall of the acini and the subsequent flattening of the epithelium tends to diminish the number of mitoses; when the pressure effects are not yet very pronounced, mitoses may still be found, but with increased pressure and flattening of the epithelium they gradually cease. This factor would thus tend to limit mitotic proliferation, especially in the iodized guinea pigs; it will, however, be necessary to make exact counts before definite data in this respect can be given.

As to the cause of the increased number of mitoses in compensatory hypertrophy, it is due to the stimulation which the lack of a sufficient amount of thyroxin in the organism sets into motion. The extraordinary increase in mitoses, which occurs in normal glands under the influence of iodine administration, is presumably due also to the direct stimulation which iodine exerts on the thyroid epithelium; but there may come into play, in addition, the effect of a slight increase in the content of the acini, which tends to stretch the acinus cells and to separate them from each other, and which thus may alter the action of contact substances by means of which neighboring epithelial cells influence each other and which normally restrict proliferative processes. Possibly also the mechanical stretching, as such, may set into motion proliferative changes. Thus a great increase in proliferative activity would be produced. How far the direct stimulation of the epithelial cells by iodine and how far a secondary process of stimulation, which primarily has called forth a slight softening of the colloid, come into play in this process, cannot be determined with certainty at the present time.

It is also of interest that iodine in compensatory hypertrophy has the opposite effect on colloid as well as on hypertrophy of the gland, which we noted in the case of administration of thyroid (Armour and Co.) (7) and of anterior pituitary substance (Armour and Co.) (8) in this condition. Both of these substances, if fed by mouth, tend to inhibit compensatory hypertrophy in the guinea pig, and to prevent the softening of the colloid, which, on the contrary, is found to be hard. The constituent of the anterior pituitary which exerts this effect is unknown at the present time; but it is probable that it is a substance which differs from those hormones of the anterior lobe of the hypophysis which stimulate the growth of the organism as a whole and which stimulate the development of the ovaries.

#### SUMMARY

Administration of potassium iodide in the guinea pig, during the process of compensatory hypertrophy of the thyroid gland as well as in the normal guinea pig, causes a stimulation of the gland tissue, in which softening and solution processes as well as increased growth processes are noticeable. In the case of the normal gland the growth processes which are initiated by iodine are very prominent, whereas in the case of compensatory hypertrophy, where the removal of a great part of the gland tissue as such causes a marked stimulation, the changes in the colloid are more pronounced. It is shown that the structural changes thus produced in compensatory hypertrophy make it possible for us in many cases to recognize whether iodine has been administered during the process of compensatory hypertrophy. The various changes induced by the administration of this substance have been discussed and also the possible relationship which these changes have to each other.

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# THE INFLUENCE OF ANTERIOR PITUITARY EXTRACT ON THE SEX GLANDS AND GROWTH

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Until recently there have been many divergent views regarding the functions of the anterior pituitary gland. The results reported by Evans (1923-24) and his co-workers led us to try some similar experiments. The following brief history of the relationship between the sex glands and growth and the anterior lobe of the pituitary gland illustrate the divergent views of the various investigators.

Schafer (1912) reported that feeding of pituitary tissue to rats had little or no effect on growth or metabolism. Wulzen (1914) claimed that fresh anterior pituitary gland, when fed to chicks, caused a retardation of growth and involution of the thymus. Goetsch (1916) stated that the feeding of the anterior lobe of the pituitary gland caused more rapid growth and earlier sexual maturity in both male and female rats. This investigator also reported that the ovary of the pituitary-fed rats had large numbers of corpora lutea. Marinus (1919) reported somewhat similar results. After feeding desiccated anterior lobe to the domestic fowl, Pearl (1916) found that there was no earlier activation of the ovary nor was there any increased egg production.

Tethelin prepared from the anterior lobes by Robertson (1916) was claimed to increase the growth of mice. These results were not confirmed by Drummond and Cannan (1921). Sisson and Broyles (1921) reported that there were no changes in the normal development of rats after feeding desiccated pituitary gland. C. S. Smith (1923) obtained negative results upon feeding the anterior lobe. These experiments were carefully controlled so that the results appear to be conclusive. That ovulation in the fowl was inhibited by intraperitoneal injections of fresh anterior lobe was reported by Walker (1925). That this result was not an effect due to intraperitoneal injections of either muscle extract or of Locke's solution was demonstrated. Feeding of fresh anterior pituitary glands to hypophysectomized rats did not prevent the changes resulting from this operation (P. E. Smith, 1927).

Crafts and Flower (1924-25) found males to remain fertile which had undergone for some months the same daily dosage of anterior hypophyseal fluid which in their sisters has led to cessation of ovulation. Evans

and Simpson (1926) found gigantism to be produced in males as well as females by such injections. By the end of the fifth month there was demonstrable a clear diminution in sex response as determined by refusal of the male to copulate with different females in active oestrus. With one exception, however, copulation was always eventually accomplished and production of healthy litters resulted. Autopsy of two cases showed great relative and considerable absolute diminution in testes weights with smaller tubules but with no evidence of degenerative changes—facts in agreement with the persistence of normal morphology of spermatazoa in the fresh ejaculate.

Evans and Long (1921) studied the effects of injections of anterior lobe hypophyseal extract on the oestrus cycle in the rat and found an immediate cessation in the four-day rhythm, smaller doses permitting oestrus to recur at longer intervals, larger doses inhibiting it altogether. On section of ovaries the characteristic picture was that of ovulation having been prevented apparently through some toxic influence exercised on the ova, but instead of follicular healing through death of granulosa and hypertrophy of the thecal cells the granulosa also had taken on growth changes and corpora lutea were produced enclosing the imprisoned ovum. In these rats either the rate of formation of corpora or their survival exceeds that typical for normal ovaries for approximately twice as much lutean substance exists in these ovaries as in normal controls. These investigators found that in addition to germ cell injury and toxicity to developing embryos there was a specific stimulant to lutean cell growth in these cases.

Since these experiments were started P. E. Smith (1927) has reported a series of investigations on the induction of precocious sexual maturity by pituitary transplants. Similar results have also been reported by Zondek and Aschheim (1927). Recently Putnam and Benedict (1928) described increased growth of skeleton and increase of the size of the nipples in a bulldog produced by intraperitoneal injections of anterior hypophyseal extract.

#### PROCEDURE

For the pituitary injections fifty-four albino rats about 30 days of age and averaging 40 gm. in weight were divided into four groups of 12 rats each and a fifth group of 6 rats. For the most part correspondingly numbered rats in each group were litter brothers or litter sisters. About half of the animals were male and the rest female. The protein injections were made into a different group of rats which had a separate control group. Five female rats were injected with a liver extract of known protein content.

An attempt was made to feed a diet adequate in every respect. The principal food of the pituitary injected rats and their controls was a mixture of casein 20 parts, butter 20 parts, dried brewers yeast 5 parts, inorganic salt mixture No. 32 3 parts, agar powder 1 part and corn starch

51 parts. This diet was given on the average five days a week. For the other two days a mixed diet of fresh lettuce, beef heart, cheese, bread and ground whole yellow corn was given with a view to supplementing any unknown deficiencies in the standard diet. The rats used for the protein injections and their controls were fed on a diet consisting of whole yellow corn, oats, milk and table scraps.

Three pituitary extracts were prepared and called Nos. 1, 2, and 3 and were injected into the animals of groups I, II, and III respectively. Group IV was a control group given no treatment and Group V was fed an amount of Extract 1 corresponding to that injected into the animals of Group I. Extracts were injected intraperitoneally every other day, one-half cc. portions being given for the first two weeks, then 1 cc. portions for 1 month and finally 2 cc. portions for the remaining injection period.

The extracts were prepared as follows:

Extract I was prepared from the carefully dissected anterior lobes of ox pituitaries.\* After grinding in a food chopper they were ground in a ball mill for 4 hours with twice their weight of 0.2 normal acetic acid. The acid was neutralized with sodium hydroxide and the precipitate formed was removed by filtration. This precipitate was dissolved in dilute sodium hydroxide and acid added to the neutral point. After filtration, the filtrates were combined and evaporated to the appropriate volume. Each cc. of the extract represented 1 gm. of the anterior lobes.

Extract II was made by adding an equal volume of saturated ammonium sulphate to Extract I before it was concentrated. After filtering off the precipitate formed it was ground with two separate portions of 50 per cent ethyl alcohol. To this alcoholic extract an equal volume of 95 per cent alcohol was added. The precipitate was placed in solution in water. Each cc. of this extract was equal to 3 gm. of the fresh gland.

In making Extract III eight volumes of 95 per cent alcohol was added to the filtrate from the precipitate used for making Extract II. As before the precipitate formed was dissolved in water. Each cc. represented 3 gm. of the fresh gland.

The liver extract was prepared by the method which Evans (1923-24) used in preparing pituitary extracts. Fresh calf liver was cut into small pieces placed in 40 per cent ethyl alcohol, the alcohol was allowed to drain, washed in sterile saline and then ground for one hour in a sterile ball mill. After adding a half volume each of sterile saturated sodium bicarbonate solution and of sterile saline, the paste was stirred. This paste was neutralized, using litmus as the indicator. After centrifuging this material, the supernatant liquid was placed in tubes. Each cc. of this extract represented about 1 gram of the fresh liver tissue. The total protein nitrogen varied from 444 to 649 mgm. per 100 cc. of extract. Before these extracts were placed in sterile test tubes, 0.1 per cent tricresol was

\*These glands were obtained as fresh as possible from the stockyards and kept on ice, but it was 24 hours or more after they were removed from the animal before they were extracted.

added as a preservative. They were kept in a refrigerator until used. All of these extracts gave the ordinary protein color tests. The injections were made intraperitoneally, using sterile syringes and needles.

Females injected with pituitary extract were observed for the development of pregnancy. At 110 days, 125 days and 150 days typical males and females from each group were killed, examined for any gross abnormalities, ovaries and testes removed, fixed and sectioned. No gross pathological changes were noted in any of the animals. The record of pregnancies is given in Table I.

TABLE I

INFLUENCE OF PITUITARY EXTRACTS ON DEVELOPMENT OF PREGNANCY

Group	No. of Animals	No. of Females Pregnant After Days					
		80	100	120	150	175	200
I	6	0	0	0	1	0	1
II	6	0	0	3	1	1	
III	6	0	0	2	1	3	
IV	4	4					
V	4	4					

*Note.*—In Group I one female killed at 110 days was non-pregnant, and two killed at 150 days were non-pregnant, and in Group II one animal died.

For determining the effect of protein injections on the sex organs and oestrus cycle, vaginal smears as well as histological sections of the ovaries were made. The technique used was that of Frank.\* A moistened toothpick was inserted into the vaginal canal and withdrawn. The toothpick was then stirred in a small drop of water on a clean slide. After drying in the air and fixing by passing through a flame several times they were stained for thirty seconds with a one per cent aqueous solution of thionin. The diagnosis of the smears was made microscopically and the classification of oestrus cycles made according to the classification of Long and Evans (1922).

The results on growth are shown in Charts I and II. In Chart I the average rates of growth of females are shown and in Chart II the average rates of growth of males. In Chart I the growth curves are terminated with the development of pregnancy. As Group V contained only six rats instead of twelve, the slightly greater growth of animals of this group, which were fed pituitary extract, is not conclusive. Nor can any favorable influence of either of the three extracts studied on growth be said to have been shown by these experiments. Evans (1923-24) in a similar period of treatment obtained differences in weight of nearly 100 grams, or 50 per cent. As Evans found the growth promoting substance to be

\*Frank, R. T. Personal communication.

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thrown down by 50 per cent alcohol, our negative results with Extracts II and III are not unexpected. Our Extract No. I was made with dilute acetic acid. The one chiefly used by Evans was an extract in normal salt solution from which the author states that most of the protein may be precipitated by making the solution 0.03 N with acetic acid without loss of hormone. One cc. of our extract corresponded to 1 gm. of fresh gland, that of Evans to 2 gm. Our injections were made every other day using about twice the daily amounts used by Evans. Evans started injections at 14

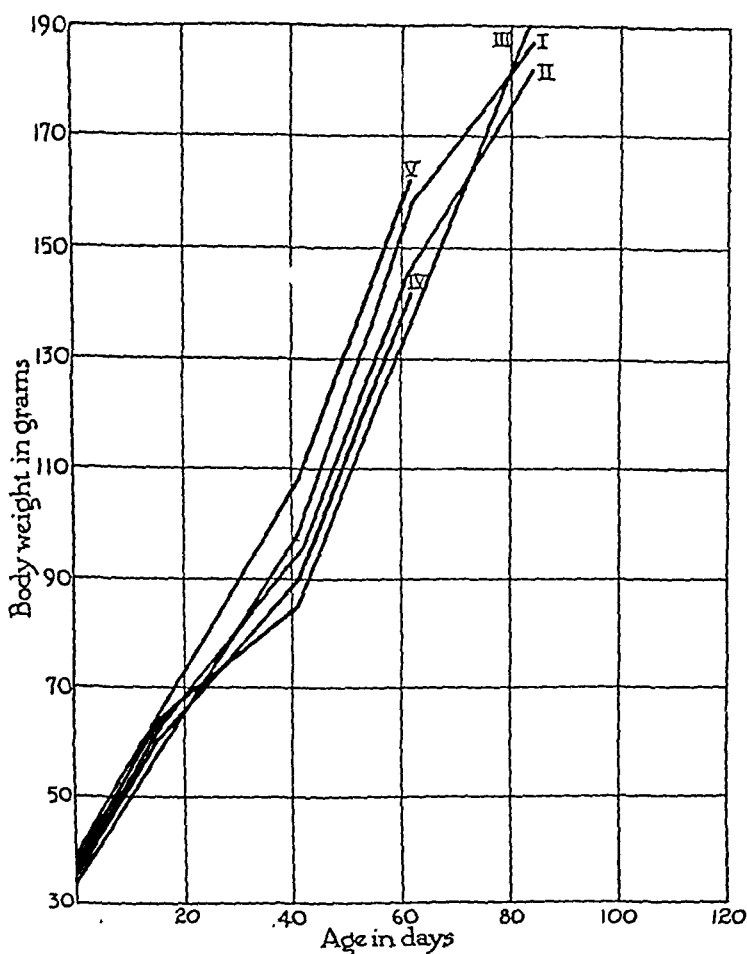


Chart I. Growth of female rats following injections of anterior pituitary extracts. Weights are averages for groups. Group IV is the control group.

days of age and we at 30 days. Our diet was planned to furnish adequate vitamine so that such substance present in the considerable amounts of extract injected could not be expected to be of influence. Evans does not describe the diet of his animals, but the controls grew well. From our results it seems as though there was actual retardation of growth rather than acceleration. Ours were acid extracts, whereas Evans made an alkaline extract which was later acidified. Though our extracts were not prepared from glands which were as fresh as those used by this investigator, the extracts were preserved with 0.1 per cent tricresol and kept cool; there

was no putrefaction at any time. For an explanation of the difference between our results and those of Evans, the most probable cause seems to be that we made an acid instead of an alkaline extract. The extract which was made by precipitating the proteins present by half saturation with ammonium sulphate, then triturating the precipitate in 50 per cent alcohol and reprecipitating a part of the soluble material by adding equal volume of alcohol, was not expected to give any growth effects. This was definitely stated by Evans. The Extract III, though it did produce some

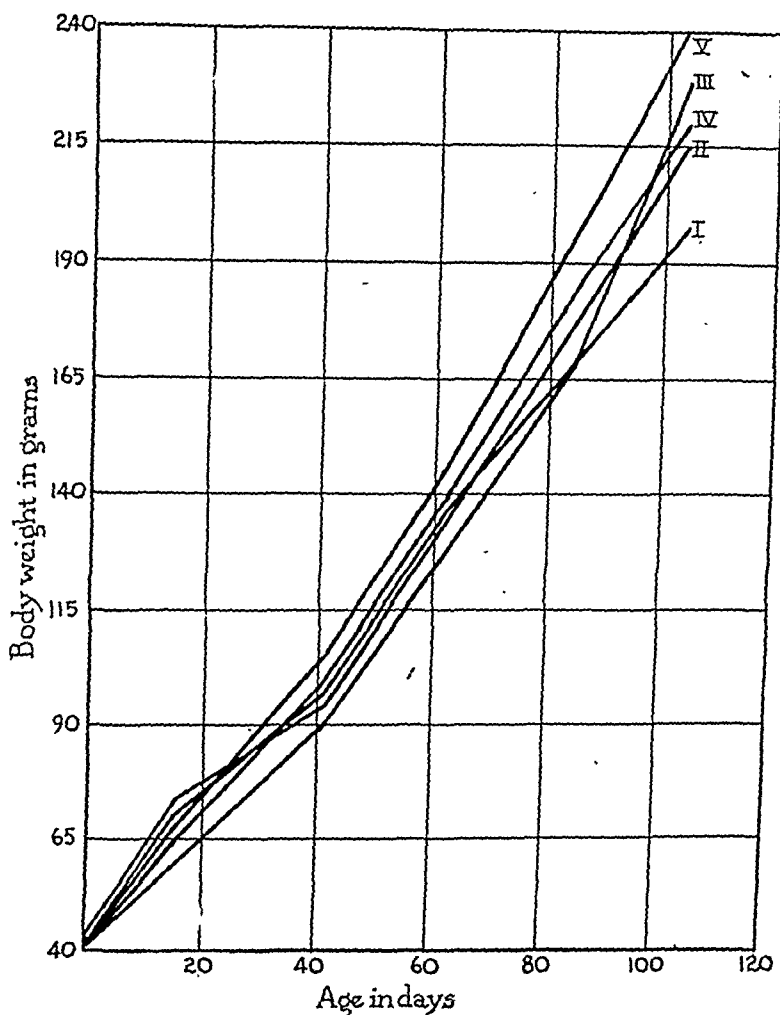


Chart II. Growth of male rats following injections of anterior pituitary extracts. Weights are averages for groups. Group IV is the control group.

retardation of pregnancy, did not, however, show much action on the ovary as judged microscopically. The liver extract was injected because it was thought that this toxic action on the ovary of the pituitary extracts was due to their protein content. The vaginal smears of these five rats showed that the oestrus cycle occurred every fourth or fifth day the same as the control rats. The retardation of the oestrus cycle described by Evans must be a specific action of the anterior pituitary extract produced when it is injected intraperitoneally into rats.

The following is a general summary of the ovarian findings: The sections of the ovaries of the rats in series I were all very similar. There were atypical Graffian follicles in various stages of development. The tunica seems to be normal. The few ova that are present are small. The granulosa has disappeared in most cases, but in some it has proliferated rather extensively. In several cases, the ova seem to be imprisoned by the rapidly proliferating cells which have come from opposite sides of the follicle so that the ova have assumed an elongated form. The cells of the corpora lutea are not of the usual large type but are much smaller and are arranged in cords separated by spaces almost equal to the cords.



Fig 1. Microphotograph of a section of the ovary of a rat receiving pituitary extract. Corpora lutea formation has been decidedly stimulated

In one of the sections in this series, the granulosa has proliferated but, instead of producing lutean cells, has failed to differentiate so that there are structureless, homogenous masses resembling hyalin excepting that they take a light blue stain. The outstanding fact about these sections is the large amount of lutean tissue and the increased numbers of atretic follicles.

From series II the sections of the ovaries show lutean cells which are arranged in the typical cell-cord manner. There were no normal follicles. The inner granulosa cells are all proliferating. In some of the larger

follicles there was evidence of degeneration in the ova toward which the lutean cells were growing. The tunica was intact but the germinal epithelium has undergone hyperplasia, as shown by the many mitotic figures, and has grown downward into the ovarian stroma.

The sections of the ovaries of Series III appeared to be normal. The follicles present were normal in number and histological structure, there being no evidence of degeneration or other atretic changes. The corpora lutea present appeared to be normal in size and structure.

The histological findings in the ovaries of the rats receiving liver extract indicate that there may be changes due to the injected proteins. The ovaries of two of the rats appeared normal microscopically, but in three of the rats there was evidence of toxic action. One of the ovarian sections showed numerous large corpora lutea nearly replacing the ovarian stroma, with an apparent diminution in the number of follicles. Another one of the ovaries exhibited abnormal proliferation of the germinal epithelium. Atresia was rather evident in one of the other ovaries.

Our findings in these ovarian sections of the rats injected with pituitary extract are very similar to those of Evans. There was a decided stimulation of lutean cells and imprisonment of the ova by lutean tissue as described by this investigator. The degeneration of the follicles in these rats was very marked. This degeneration of the follicles must lead to an inhibition of ovulation. There must have been some inhibition of ovulation because but few of the rats in series I became pregnant. The rats in series II also became pregnant later than those in series IV and V. The ovaries of the rats in series III did not seem to be affected by the injections and consequently, pregnancy was not deferred as much as in the two previous groups. The deferring of pregnancy was greater in group I than in the other two groups. The degeneration of the ovaries in this group was greater than in the other two groups. Our results are not in agreement with those of Putnam, Teel and Benedict (1928), who claim that acid extracts have little or no activity. We have observed the same retardation of pregnancy and ovarian changes that have been described by Evans and confirmed by Bellerby (1928).

Since Oslund (1926) has shown that protein injections may lead to degeneration of the seminiferous tissue, we thought protein injections intraperitoneally might cause some changes in the ovary. The oestrus cycles of the five rats which were injected with liver protein were normal compared with the results of Long and Evans (1922). The length of the oestrus cycles in these rats was the same as the control group of six rats. Though these results are not as decided as those reported by Evans we feel that they should not be overlooked. Since the protein content of his extracts was not determined we are not certain that we were injecting equivalent amounts of proteins. But in no case was the oestrus cycle retarded, even if there were evidences of ovarian injury. That oestrus may not be dependent on the follicles is stated by Parkes (1927), who sterilized mice by means of the x-ray. Such animals still had normal oestrus cycles.



This author believes that the synchronization of ovulation and oestrus is probably due to a common stimulus.

The testes of the rats receiving injections show active spermatogenesis but there was more than the normal amount of degeneration of the germ cells, especially of the intermediate stages of spermatogenesis, i.e., the spermatocytes. The sustentacular and interstitial cells were normal in number and structure. The testes of series IV and V were normal in every respect.

The weights of the testes of the rats receiving injections were less than those of the controls. This may, however, be attributed to the lower weights of these rats. This is not attributed to any specific effect of the pituitary extract but may be due to the proteins injected as Oslund (1926) has shown that injections of this type may lead to degeneration of the seminiferous tissue. From his results as well as our own we feel that the result may be a protein effect and not specific for any tissue extract. This degeneration of spermatogenic cells was, of course, not marked, as the females in these cages became pregnant. The weights of the testes of the normal rats compare favorably with weights according to Donaldson (1924) but the testes of the injected rats are definitely below the normal weight.

The results reported in this paper cannot be due to diet, nor any other factors than the injections. The coats of the animals were sleek and they appeared to be healthy in every way. The diets were evidently adequate in both sets of experiments because the weights of the controls were always above the normal. The reproduction and oestrus cycles of the animals not subjected to the injections were normal.

#### SUMMARY.

1. Albino rats injected intraperitoneally with acetic acid and alcoholic extracts of the anterior lobe of beef pituitary glands did not show any more rapid growth than the controls.
2. A substance or substances having a toxic action on ovarian follicles is present in the anterior pituitary gland extracts as prepared.
3. This toxic material is soluble in 50 per cent alcohol.
4. The toxic action exerted upon ovarian follicles by intraperitoneal injections may be due to the protein content.
5. Some degeneration in the ovary does not increase the length of oestrus cycle in the rat.

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# DEMENTIA PRECOX AS AN ENDOCRINOPATHY WITH CLINICAL AND AUTOPSY REPORTS\*

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## LITERATURE

The literature contains many references to the changes of the endocrine glands in dementia precox. Kraepelin (1) in 1881 first called attention to the relation of this disease to the endocrines, especially to the sex glands.

Dercum (2) postulates that in dementia precox the various glands of internal secretion have suffered in the course of the development of the organism so that their respective functions are subsequently imperfectly and aberrantly performed. He feels that it is not at all unlikely that, while a number of glands, perhaps the entire chain, are involved in most cases, e.g., the gonads may dominate the picture, in others again it is the thymus; in still others it is the system of the pituitary, thyroid and adrenals. He regards the thymus as most likely to be involved because cases of dementia precox frequently betray in childhood the forerunners of the affection.

From the histological study of two cases Kojima (3) concludes that the thyroids have an opposite appearance in the male and female; a tendency to hypofunction in the male and hyperfunction in the female. He states that in dementia precox the glands, on the whole, are small, especially in the female. In the male the parathyroids contain watery, clear cells and a few eosinophile cells, and in the female on the contrary many eosinophile cells. The sexual glands and adrenals are small in the female. Striking changes are seen in the sexual glands, i.e., very slight spermatogenesis in the testes and an appearance of early involution of the ovaries.

Fränkel (4) found the infantile type of genitalia in 72 per cent of 176 cases of dementia precox cases examined, and Mott (5) showed pathologic changes in the testes and semen, defective maturation of the primordial follicles, degeneration of the nucleus and proliferation of the stroma, so that he believed that dementia precox results from deficient productive energy of the generative organs, based on congenital insufficiency of the gonads. He found a primary regressive atrophy in 27 cases of dementia precox in which the testes were examined.

Pézar (6) states that apparently the testes in the schizophrenic cease growing about the age of puberty, or soon after, thus allowing sufficient time in most cases for secondary sexual characteristics to develop, although

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\*Work done at the Blackburn Laboratory, St. Elizabeth's Hospital, Washington, D. C., and paper read before the Washington Clinico-Psychopathological Society, March 19, 1928.

these are always fully determined. Pézard in experimenting on the gonads of fowls, found that as little as a thirtieth of the testicular tissue left in the body permits development of the secondary sexual characteristics.

Matsumato (7) in a study of the relation between the reproductive organs and dementia precox, and Lewis (8) after a careful review of the autopsies of 143 cases of this disease as compared to 458 other autopsies, concludes that gonadal atrophy is more commonly found in dementia precox cases than in other individuals. Also, that in these cases the adrenal cortex as a whole is thinned out and pale in color. The zona glomerulosa is rudimentary and sclerotic, and the zona fasciculata shows acinal and cellular alterations. Unfortunately most of the authors take the degree of spermatogenesis as the criterion of degeneration of the endocrine function of the testes, which is an erroneous basis, as will be later pointed out.

Morse (9) studied 12 male and 15 females schizophrenics dying under 45 years of age, and concluded that 16 patients had active gonads. She used as criteria the presence of spermatogenesis and maturing follicles and corpora lutea. She states that there was no correlation between atrophy of the sex glands and the duration of the mental disease or the degree of psychic deterioration. The conditions in the sex glands of the controls were essentially the same as in the dementia precox cases for the same terminal diseases. The pituitaries in nearly half the cases presented a fibrosis, which could be correlated to some extent with similar condition in the gonads. This fibrosis of the pituitary is not peculiar to dementia precox but depends rather on the nature and the duration of the terminal disease. She states that the lesions in the adrenals were such as are usually found in the diseases to which the patients succumbed. The thyroid showed changes less frequently than the other endocrines. There was occasionally a mild, glandular hyperplasia or increase of connective tissue. From the pathologic side Morse feels that there is very little evidence of primary atrophy of the gonads in dementia precox, with the possible exception of those cases developing on a basis of mental defect.

Geller (10) attempted to show the close relations between the body and psyche in dementia precox on the basis of sexual function. He found considerable anatomic and functional hypogenitalism in 7 of 8 cases of dementia precox in women, and agrees with Mott, Frenkel, Hauck and Kohler that the disorder is intimately associated with deficient genital function. Serologic tests in these cases were found by Geller to show destruction of the brain, testes, ovary and often also of the thyroid substrates more frequently than in other psychoses. In 26 women his most important finding was that at the age of sexual maturity the genital organs were hypoplastic. Thus he feels justified in assuming a connection between inferior ovarian function and dementia precox.

Tsubura (11) in 1923 reported that individuals without gonads showed a lowered tolerance for sugar, and that if these individuals were given subcutaneous injections of either adrenalin or pituitrin, a marked hyper-

glycemia followed. He also found that if gonads were transplanted into these individuals, the above conditions were eliminated.

Benon (12) concluded that schizophrenia can be considered as a dementia, but should be regarded as a dysthymia, due to causes outside the brain.

Walker (13) states that the pituitary and adrenals are most important in the determination of the sex characteristics, and that the interstitial cells of the gonads are trophic rather than secretory. The following year Korenshevsky (14) reported that 60 per cent of castrated individuals become obese, while the remaining 40 per cent are usually thin. He found that in these cases the nitrogen metabolism is decreased. Lipschütz (15) states that the morphological and physiological changes which follow absence or deficiency of the gonads vary according to the age at which the deficit arose. He found that the thyroid of the hypogonad subject was usually small and that the hypophysis was larger and heavier than in normal individuals.

In order to prove whether the ovaries play a part in dementia precox, Pötzl and Wagner (16) removed the adnexa in two cases of long standing. Fibrosis such as described by Frankel in the testes of male schizophrenics was found in the ovaries. Hypothetically, a delay in the retrogression of the corpora lutea may be assumed as a manifestation of injury to the genital glands in female schizophrenics, they state, which is to a certain extent comparable to a pregnancy action. These workers had no favorable results from castration combined with homioplasic ovarian grafts in schizophrenic women. They attribute the menstrual aggravation to increased permeability of the meninges during these periods.

According to Sippel (17) a more or less pronounced hypoplasia and hypofunction of the sex glands is found in a considerable percentage of dementia precox cases. In a few cases he tried transplantation of ovaries in treatment of schizophrenia. In one case he obtained no results. Three subjects improved to a surprising extent.

Gibbs (18) found that some disturbance of lipid metabolism may occur in dementia precox and may involve the suprarenal cortex as suggested by the following: (a) Previous observations on the sexual development and behavior of these patients; (b) the evidence that the suprarenal cortex is involved in these disturbances of sexual development; (c) the evidence that the suprarenal has both an embryologic and functional relation to the gonads on the one hand and to the brain on the other; (d) substances of a lipid nature play an essential part in the functional metabolism of each of these organs; (e) the female sex hormone and the vitamine for reproduction are both of a lipid nature; (f) the low basal metabolism rate frequently observed in dementia precox suggests an involvement of the suprarenals. He also found that in many patients with dementia precox the blood cholesterol was unusually low, and may be more directly

correlated with the psychosis and with sex than with any other recognized factor.

Münzer (19) describes in detail the case of a man of 25 years who quite suddenly developed a schizophrenic state with delusions, chiefly in the sexual sphere, and after three months committed suicide. The chief gross changes at autopsy consisted of enlargement of the thymus, which weighed 50 grams and showed marked increase in the number and size of Hassall's corpuscles; enlargement of the spleen and of the lymph follicles of the tongue and small intestines. The testes weighed 32 grams and showed marked atrophy and degeneration and abundant Lubarsch-Charcot crystals. The adrenals weighed 17 grams, with rather hypertrophic cortex and persistent undifferentiated cells of the zona glomerulosa of the cortex. There was reduction of the islands of the pancreas, and the thyroid presented a polymorphic picture, with good evidence of function, even hyperfunction, but also degenerated foci resembling those seen in idiots and cretins. One of the parathyroids lay within the thyroid; there was diminution of eosinophile cells, and on the whole these glands had preserved the characters seen in children. There was apparent increase in the eosinophilic cells in the hypophysis and an adenoma-like formation. Münzer maintains that abnormalities of the endocrines are constant in this psychosis.

The most complete recent study of the problem is by Langfeldt (20), who reports a detailed clinical examination of 40 unquestionable cases of dementia precox. He used every known diagnostic test of any value. His cases fell into three groups: 16 catatonic, 11 hebephrenic, and 13 mixed. In the catatonic group he found the following essential disturbances present in both the acute and the quiescent cases: slow pulse, low blood pressure, lymphocytosis, glandular swelling, positive pilocarpin test, positive Aschner reflex (vagotonic signs), and reduced basal metabolism. In the acute cases he noted also certain sympathetic signs such as dilated pupils, tachycardia, exophthalmos, and reduced glucose tolerance. In the hebephrenic cases, in the acute as well as the chronic phases, only sympathetic symptoms were found: tachycardia, exophthalmos, tremor, dilated pupils, and reduced glucose tolerance. These symptoms were, however, found most pronounced in the acute phases. In hebephrenia he found a normal basal metabolism and normal blood picture, apart from eosinopenia in the acute phases. In the hebephrenics he also found large firm testes.

Bowman (21) studied 24 cases of schizophrenia, both male and female, and found an abnormally low basal metabolism in 50 per cent, with a tendency to low or minus reading in nearly all the rest of the cases. Nearly one-half showed an abnormal blood sugar curve, all but one being of the "sustained" type. Over one-third showed a positive galactose test. X-ray studies and gastric analyses showed a definite functional disorder of the gastro-intestinal tract in about half of the cases and questionable functional disorders in all but two of the others. Radioscopy revealed

infected teeth in 40 per cent and questionable infection in 10 per cent more; "dropped" hearts in 30 per cent; questionable pulmonary tuberculosis in 13 per cent and healed pulmonary tuberculosis in 4 per cent more. The ovaries had been removed in several, and a number gave histories of severe illness in childhood.

#### EUNUCHS AND SCHIZOPHRENIA

While in China during 1925-27 I had opportunity to examine twenty Chinese eunuchs abandoned after the dissolution of the Imperial Court in Peking, and three Skopecs driven from Russia and taking refuge in China. The former type of eunuchs have been known in China as long as history, and were used as servants in the Imperial Palace. Many of these were castrated in youth, and were completely deprived of external genitals (23). The Skopecs were castrated because of their religious teachings and it is said that there were at least 150,000 members of this sect before the intolerance of the Soviet scattered them out of Siberia. This sect has been in existence since 1757, and many of the subjects were castrated in childhood. Two of the Skopecs examined had their external genitals completely removed, while the third had only been castrated. Female members of this religion may be only spayed, or their breasts may also be removed. Unfortunately for this record, no female Skopecs were seen in China.

All of the twenty-three eunuchs examined showed certain general characteristics. Fifteen tended to be obese and 8 were emaciated, probably due to starvation. The larynx was infantile. The extremities were proportionately larger than normal. In all cases it was found that the body height: leg length ratio was 1.75, whereas in an equal number of normal individuals it was 2.0. The pelvis was juvenile. There was an acrocynosis and the nails were spotted. Several showed a rather general cyanosis of the body, while the remainder were very pale. The skin was clammy, rather puffy, doughy, and creased. The subcutaneous fat in the gluteal region, under the breasts, in the trochanters, abdominal wall, and especially under the mons veneris, was more abundant than in normal men. The middle of the upper lip, the submental skin, the cheeks and the upper part of the neck were hairless. The perineum, axillae, and extremities did not have the abundant hair that is commonly found in the normal male. The pubic hair line was horizontal, or, in 2 or 3 of the individuals, concave.

Psychologically these individuals were found to all have good intelligence, were all orientated, but had been living a hand-to-mouth existence since they had been thrown on their own resources. They all appeared very introspective and apathetic. Although they could talk quite intelligently when questioned, they never volunteered any information, and appeared very stupid. They seemed methodical in their actions, and only two showed any purposeful efforts. There was a distinct lack of affect;

they were cold and passive, although in dire straits financially. At least half of the eunuchs had got into trouble because of their tempers, and two had been sentenced because of murder. They all appeared moody. Most of the eunuchs who still retained the penis stated that they had often indulged in sexual intercourse with prostitutes, although they had found that their erections were always of short duration. They all said that they indulged in homosexual practices and other perversions. Ten of them had had gonorrhea and one had an active chancre. Unfortunately no blood examinations or basal metabolism tests could be made on these subjects, but Shen and Lin (24) have reported the nitrogen metabolism of eunuchs examined by them, and it conforms to the general picture.

Because the examination of these eunuchs showed them to be almost typical prototypes of what is considered "dementia precox," it was decided to make an examination of the autopsy material of diagnosed "dementia precox" cases recorded at Saint Elizabeth's Hospital, and to examine a large number of "dementia precox" patients under care at the Government hospital for mental diseases, and to see if the symptom-picture remained constant.

#### CLINICAL EXAMINATION

In order to determine a normal somatic standard, 50 normally reacting males and 24 normally reacting females between the ages of 16 and 50 years were first examined. The individuals were seen during the routine examination for life insurance and could all be classed as normal healthy individuals.

In selecting the patients the various services at the hospital, which cares for 3960 psychopaths, were asked for a list of cases considered without doubt to be typical examples of "dementia precox," and 70 of these males and 40 female cases were given careful physical examinations.

#### *Males*

The males ranged between the ages of 18 and 48 years, but 77.1 per cent were under 30 years of age and all appeared in good physical health. Of this number, 38.8 per cent were of the thin type, and 27.7 per cent were obese. Five and a half per cent showed acrocynosis and most of them appeared rather pasty; 11.1 per cent had polyuria, 5.5 per cent increased salivation, and 5.5 per cent showed dermatographism.

Sixty per cent were found to have female distribution of hair, 38.5 per cent had a penis smaller than normal, while 22.8 per cent had a penis larger than normal. Only 5.7 per cent had apparently normal testes, all the rest being smaller, larger, softer, harder, etc., than normal; 68.5 per cent showed more or less disease of the prostate. Forty per cent were circumcised or had a retracted prepuce.

Of the five married patients, three had children, totaling eight in number. Two of the single patients definitely knew they had had chil-



dren. Of all the patients, 43 per cent showed unmistakable signs of masturbation; 5 of the men had undoubtedly abused themselves to excess, while 2 had questionably indulged in this practice. About 50 per cent had occasionally had coitus before coming to the hospital, and 50 per cent continued to have an occasional orgasm with extrusion of semen, either mechanically or during erotic dreams. About 7 per cent had very infrequent orgasm, while 8.5 per cent had one or more orgasms daily while in the hospital. Only 20 per cent said they had desire for heterosexual practices.

At least 40 per cent of the patients had a history of gonorrhea and 10 per cent had a history of syphilis. Over 22 per cent had had a severe toxic illness before the onset of the psychosis. The severe attacks recorded were diphtheria, yellow fever, malaria, small-pox, mumps, scarlet fever, and influenza. Of all the patients, 5.5 per cent had been known as "weak children"; an equal number had one psychopathic parent; another 5.5 per cent had been heavy drinkers before the onset of the psychosis.

There is plenty of authority to substantiate the fact that the toxemias have a very deleterious effect on the endocrines, and some, such as mumps, appear to have a selective effect on the gonads. The adrenals are known to be especially sensitive to toxins.

The fact that a person is able to have an erection or even to have an orgasm is no criterion of the endocrine state of his testes. Erection may not be associated with sexual desire, for priapism may be a sign of cervical injury, myeloid leukemia or tabes, even though the testes have been removed. Then, again, the reflex centers may have acquired the mechanism of erection before the loss of the sexual stimulation, as was shown by the foregoing report concerning eunuchs. As to extrusion of semen, this may take place without erection, simply as a reflex emptying of distended vesicles.

From the reports concerning the *Mujerados* of Mexico it may be concluded that excessive extrusion of semen causes atrophy of the gonads. These individuals, descendants of the Aztecs, are masturbated to orgasm several times daily until testicular degeneration takes place. These men become virtually eunuchs and acquire the characteristics of the latter. They are used as menial servants. It is possible that the history of sexual excess in the schizophrenics examined may account for some of the gonadal dystrophy found, although, as will be later shown, the moderate practice of masturbation is conducive to continuation of spermatogenesis.

### *Females*

The female patients examined ranged between 16 and 47 years of age, but 87.5 per cent were between 20 and 40. The onset of the first signs of psychosis was recorded as being between 10 and 18 years of age in most of the cases. Seventy-five per cent of the women were married.

The majority were of the thin type; 22.5 per cent showed male distribution of hair; 7.5 per cent had hypertrophied external genitals; 12.5 per cent had large pendulous breasts; 17.5 per cent small infantile breasts; 10 per cent, flat breasts; 2.5 per cent had normal appearing breasts but after pregnancy did not lactate; 7.5 per cent had extremely large breasts.

Fifty per cent had amenorrhea, 14.3 per cent vicarious menses, 14.3 per cent profuse menses, 7 per cent irregular periods, 28.5 per cent dysmenorrhea, and 7 per cent scanty menses. Thirty-five per cent had been pregnant one or more times, 25 per cent had had miscarriages, and 12.5 per cent had normal births; 5 of the women had 11 children. Of all the subjects, 7.5 per cent were distinctly homosexual, 2.5 per cent had excessive sex desire, and an equal number had had precocious sex development.

On bimanual examination and from past history of operations it was found that 52.5 per cent of the women had unmistakable ovarian disease, 42.5 per cent had uterine trouble, 25 per cent had had ovariectomies, and 2.5 per cent showed infantile uteri. Five per cent showed first signs of psychosis during pregnancy and 2.5 per cent showed definite venereal infection.

Fifty-five per cent of the patients had had serious illness before psychopathic symptoms: 27.2 per cent of this number had a severe attack of measles; 27.2 per cent, scarlet fever; 18 per cent, malaria; 18 per cent, pertussis; 13.6 per cent, diphtheria; 9 per cent, mumps; 9 per cent, typhoid; 4 per cent, influenza; 4 per cent, pneumonia; 4 per cent, inflammatory rheumatism; 9 per cent, peritonitis; 27.2 per cent had been undersized or delicate as children.

#### AUTOPSY STUDIES

A detailed study of 487 autopsies was made to determine if there were any biometric and microscopic differences between the cases diagnosed as *dementia precox* and the other psychoses. Of this number, there were 158 male (between the ages of 19 and 97), and 24 female (between the ages of 21 and 85), "*dementia precox*" cadavers, and 241 male (between the ages of 21 and 97), and 64 female (between the ages of 15 and 86), cadavers dying at Saint Elizabeth's Hospital without the diagnosis of "*dementia precox*."

All the cases were divided into age groups: 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, and all over 70 years. The cases with the diagnosis of "*dementia precox*" were separated into catatonics, hebephrenics, and mixed. The last group included all those diagnosed paranoid, simple, or undifferentiated.

#### Male Autopsies

The males examined in the schizophrenic group ranged in age from 19 to 97 years; 11 per cent were between 20 and 30, 18 per cent between 30 and 40, 20 per cent between 40 and 50, 18 per cent between 50 and 60, 17 per cent between 60 and 70, and 16 per cent over 70 years old. None of the catatonics were over 50 years of age. The *dementia precox* patients had been in the hospital from 6 months to 54 years; their records showed the onset of insanity to be anywhere from 18 to 55 years of age. Of these cases 24.5 per cent were of the catatonic type; 39.5 per cent, hebephrenic; and 36 per cent, mixed.

Tuberculosis in some form was responsible for the death of 39.9 per cent of the schizophrenics, while it was the cause of death of only 8.3 per cent of the other psychotics. Pneumonia caused the death of 27.7 per cent of the *dementia precox*, and 56 per cent of the other subjects. Myocarditis was the lethal disease in 12.3 per cent of the schizophrenics and 35 per cent of the others. All the category of

diseases could be found in the other cases not included in the above percentage, although 67 per cent of the dementia precox subjects showed myocardial degeneration.

Of the schizophrenic males, 51.25 per cent were thin; only 10 per cent were obese; the remaining 38.75 per cent were within normal limits of weight.

Eighty per cent of the schizophrenics showed female hair distribution; 42.5 per cent were circumcised or had retracted prepuces; 62.5 per cent showed obvious signs of masturbation.

The brain in 31.1 per cent of the schizophrenics was found to be normal in all respects, while only acute or minor degenerative changes were found in the remaining 68 per cent. The meninges appeared thinner than the average in 55.5 per cent of the brains. The 20 to 30 year dementia precox group showed an average brain weight of 1314 grams as compared to 1281 grams in the other psychotics; from 30 to 40 years, 1263 grams as compared to 1276 grams; 40 to 50 years, 1328 grams as to 1284 grams; 50 to 60 years, 1393 grams as to 1260 grams; 60 to 70 years, 1236 grams as to 1241 grams; and over 70 years, 1213 as to 1170 grams.

The hypophysis was normal in 42 per cent of the dementia precox autopsies, 38 per cent were atrophic or sclerotic, 5.2 per cent cystic, and only one was hyperplastic. This gland in the 20 to 30 year group gave an average weight of 605 mgm. as compared to 725 mgm. for the non-schizophrenic individuals; 30 to 40 years, 691 as to 698 mgm.; 40 to 50 years, 737 as to 681 mgm.; 50 to 60 years, 634 as to 667 mgm.; 60 to 70 years, 660 as to 655 mgm.; and over 70 years, 623 as to 606 mgm. The schizophrenic glands showed an average cell content of 43 per cent eosinophiles, 17 per cent basophiles, and 40 per cent neutrophiles, with 20 per cent of the glands showing the relation 55-10-35, and an equal number, 35-10-55, with 16 per cent showing 30-20-50. The non-schizophrenic glands gave an average of 52 per cent eosinophiles, 28 per cent basophiles, and 20 per cent neutrophiles, with 24 per cent of the glands giving the relation 45-35-20; 20 per cent giving 60-20-20; 16 per cent 70-15-15; and 12 per cent 30-50-20.

The pineal was found to be normal in all respects in 46 per cent of the dementia precox cases, while 38 per cent showed an atrophic, sclerotic, or fibrosed gland. Biometrically there was nothing to be noted.

The thymus showed fatty degeneration in 54 per cent of the dementia precox cases. This gland in the 20 to 30 year old individuals gave an average weight of 8.4 grams with 17.1 per cent active tissue present, as compared to 14.4 grams and 40 per cent activity in the non-schizophrenic cases of this age; 30 to 40 years showed 8.68 grams and 15 per cent activity as compared to 10.5 grams and 24.6 per cent; 40 to 50 years, 10.8 grams and 11.9 per cent as to 11.25 grams and 7.5 per cent; 50 to 60 years, 19.5 grams and 12.7 per cent as to 19.7 grams and 2.4 per cent; 60 to 70 years, 18.19 grams and 2.27 per cent as to 26.18 grams and 6.54 per cent; and over 70 years, 11.5 grams and 1.56 per cent as compared to 12 grams and 3.7 per cent activity.

The thyroid was found to be normal in 39 per cent of the dementia precox cadavers, hypertrophied in 6 per cent, and atrophied or fibrosed in 43.2 per cent. Most of the normal glands were found in the catatonics. From 20 to 30 years the catatonics showed an average thyroid weight of 10.12 grams, hebephrenics 26.4 grams, mixed type 27 grams, with a general average of 19.3 grams as compared to 22.74 grams in the non-schizophrenic cases; 30 to 40 years, 20.8 grams, 18.6 grams, and 20.39 grams, respectively, with an average of 19.79 grams as to 24.14 grams; 40 to 50 years, 28.75 grams, 24.99 grams, 23.73 grams, respectively, with a general average of 25.2 grams as to 41.58 grams; 50 to 60 years, a general average of 19.33 grams as to 28.05 grams; 60 to 70 years, 23.22 grams as to 25.55 grams; and over 70 years, 22.76 grams as to 22.22 grams.

The parathyroid glands in 44 per cent of the dementia precox cases were found to be normal, 30 per cent showed fatty infiltration, and 26 per cent atrophy or fibrosis. The weight of these glands was not significant.

The pancreas showed nothing striking. Forty-four per cent of these glands found in the dementia precox cadavers were normal, 17 per cent showed fatty infiltration, 13 per cent fibrosis, and all the rest acute or autolytic changes.

The adrenal glands revealed some rather remarkable changes, as only 25.3 per cent of the glands could be classed as normal. One old schizophrenic 60 years of age had hypertrophy of the medulla, two others, 67 and 58 years of age, had hypertrophy of the cortex, and one subject, 30 years of age, who had the beginning of his psychosis when 27 years old with a diagnosis of hebephrenic type had hypertrophy of both the medulla and cortex, and a degeneration of the testes. The rest of the glands examined were atrophic. From 20 to 30 years, the cata-

tonics gave an average weight of 7.02 and 6.42 grams, respectively, for the right and left adrenals; the hebephrenics, 5.93 and 7.13 grams; mixed, 7.6 and 7.6 grams, with a general average of 6.81 and 6.87 grams as compared to 6.5 and 7.6 grams for the control cases. From 30 to 40 years the weights were 6.8 and 7.76 grams, 7.2 and 7.34 grams, 5.98 and 7.54 grams, with a general average of 6.67 and 7.51 grams as compared to 7.19 and 7.69 grams; 40 to 50 years, 6.13 and 6.53 grams, 7.7 and 8.85 grams, 6.7 and 7.33 grams, with a general average of 6.87 and 7.57 grams as to 7.41 and 7.74 grams; 50 to 60 years, a general average of 5.91 and 6.12 grams as to 7.06 and 7.95 grams; 60 to 70 years, 8.23 and 10.26 grams as to 6.06 and 7.03 grams.

The prostate was hypertrophied in slightly over 50 per cent of the dementia precox cases; 9 per cent were congested; 5.4 per cent atrophied; 14.5 per cent were normal.

The most interesting findings in the endocrine system of the dementia precox cadavers were seen in testes, in that only 4.4 per cent of these glands were normal and this small percentage might quite well be accounted for by the errors of psychological diagnosis. Thirty-four per cent of the testes were fibrosed and 61.6 per cent were diagnosed chronic interstitial orchitis. From 20 to 30 years the testes gave an average of 12.08 and 11.46 grams, respectively, for the right and left gonads in the catatonic group; 11.25 and 10.27 grams for the hebephrenic; 14 and 11.5 grams for the mixed cases; and a general average of 12.21 and 11.1 grams, with 42.6 per cent of the testes showing chronic interstitial orchitis, 42.6 per cent atrophy, and only 14.8 per cent were apparently normal; while the non-schizophrenic testes of this age gave 11.92 and 11.12 grams, respectively, and 80 per cent were normal while 20 per cent showed parenchymatous degeneration. From 30 to 40 years the catatonics gave a weight of 12.25 and 9.28 grams, the hebephrenics 10.99 and 9.94 grams, and the mixed 12.22 and 12.21 grams, with a general average of 11.76 and 10.59 grams, 40 per cent chronic interstitial orchitis, 30 per cent atrophy, 20 per cent fibrosis, and 10 per cent minor degenerative changes, as compared to 13.79 and 14.68 grams in the controls, 28 per cent of the glands showing chronic interstitial orchitis; 16 per cent, atrophy; 8 per cent, fibrosis; 4 per cent, parenchymatous degeneration; and 44 per cent being normal. From 40 to 50 years the findings were 12.55 and 13.38 grams, 12 and 11.24 grams, 14.08 and 13.56 grams, with a general average 13.16 and 12.86 grams, and 18.2 per cent chronic interstitial orchitis, 45.5 per cent atrophy, 36.6 per cent fibrosis, as compared to 15.2 and 14.2 grams, and 18.2 per cent chronic interstitial orchitis, 18.2 per cent fibrosis, 9 per cent atrophy, and 4.5 per cent parenchymatous degeneration. In the 50 to 60 year group there was a general average of 15.08 and 14.09 grams weight, and 55.6 per cent fibrosis, 22.3 per cent chronic interstitial orchitis, 11.1 per cent sclerosis, and 11.12 per cent atrophy, as compared to 14.98 and 13.26 grams and 33.3 per cent fibrosis, 16.7 per cent chronic interstitial orchitis, 16.7 per cent atrophy, and 33.4 per cent parenchymatous degeneration. In the 60 to 70 year group the findings were: 14.7 and 15.7 grams, with 25 per cent chronic interstitial orchitis, 50 per cent atrophy, 12.5 per cent fibrosis, and 12.5 per cent parenchymatous degeneration, as compared to 13.1 and 12.8 grams, and 10 per cent chronic interstitial orchitis, 40 per cent atrophy, 30 per cent fibrosis, and 20 per cent parenchymatous degeneration in the controls. Over 70 years old, the glands showed 11.68 and 10.73 grams and 50 per cent atrophy, 40 per cent fibrosis, and 10 per cent chronic interstitial orchitis, as compared to 13 and 11.9 grams, and 50 per cent atrophy, 11.1 per cent fibrosis, 33.3 per cent chronic interstitial orchitis, and 5.6 per cent parenchymatous degeneration.

In studying the testes, as mentioned before, unfortunately pathologists have taken the presence or absence of active spermatogenesis as the criterion of functioning or non-functioning testes. The trend of the available evidence is to the effect that the incretion of the gland is mediated, not by the spermatogenic but by the lipoidal type of interstitial cells between the spermatid tubules. The presence or absence of this constituent is the true criterion of the endocrine activity. Spermatogenesis is dependent on sexual activity, although shrinkage of the interstitial substance may cause occlusion of the spermatid tubules and thus an atrophy. Subjects, whether of dementia precox or not, who indulged in moderate sexual stimulation, either by coitus or masturbation, showed active spermatogenesis in spite of age. Retention of the spermatozoa caused atrophy, and over stimulation appears to cause degeneration by fatigue. Testes of the control subjects, although in many cases containing no spermatozoa, still had varying amounts of interstitial elements, while masturbating or sexually active schizophrenics, although having apparently normal spermatogenesis, had testes containing little or none of the lipoidal substance.

*Female Cadavers*

Of the 24 female dementia precox cadavers examined, 20 per cent were of the catatonic type; 35 per cent, hebephrenic; and 45 per cent were mixed. Of all subjects, 58 per cent were legally married, 8 per cent had been in "free-love" marriage, and 34 per cent were single. All but two of the married women had children, having from 1 to 5 each, and one of the single women had had a miscarriage. The histories revealed that the psychoses developed between the ages 17 and 52 years, while about 80 per cent of the women developed their psychoses before 39 years of age.

Thirty per cent gave a history of a severe attack of measles some time in their lives; 20 per cent, scarlet fever; 10 per cent, typhoid; 10 per cent, diphtheria; 10 per cent, mumps; and 10 per cent, influenza; 10 per cent had had chorea, 30 per cent showed histories of alcoholism in one or both of the parents, 20 per cent had parents that were psychotic, 10 per cent had had miscarriages, and 30 per cent dated the psychosis from pregnancy. Only three subjects gave menstrual histories; one woman of 35 years, with grossly normal reproductive organs, had had amenorrhea for the last 4 years before death; another had had amenorrhea for 20 years before death, and another, of 34 years, had had irregular menses and dysmenorrhea all her life.

The primary cause of death in 25 per cent of the dementia precox women was myocarditis and another 25 per cent, pneumonia; 20 per cent had streptococcus septicemia, 15 per cent tuberculosis in some form, and 15 per cent carcinoma. Of the control psychotic group, 43 per cent died of myocarditis; 30 per cent, pneumonia; 13 per cent, neurosyphilis; 9 per cent, tuberculosis; and the remaining 5 per cent died of septicemia, encephalitis, etc.

Of the total number of females coming to autopsy, 21 per cent of the dementia precox and 6 per cent of the control subjects were between 20 and 30 years of age at death; 17 per cent and 8 per cent, respectively, between 30 and 40 years of age; 8 per cent and 8 per cent between 40 and 50 years; 21 per cent and 16 per cent between 50 and 60; 8 per cent and 19 per cent between 60 and 70; and 25 per cent and 43 per cent over 70 years of age. There were no catatonics over 50 years old.

As compared to 61 normal females, 45 per cent of the dementia precox cadavers were thin, 25 per cent were obese, 20 per cent higher, and 40 per cent shorter than normals of the same age, while of all the other female psychopaths coming to autopsy 52 per cent were thinner than normal, and 17 per cent were obese. Slightly over 14 per cent had scanty hair growth, while 28.5 per cent had male distribution of hair, 43.8 per cent had atrophic breasts, 6.2 per cent had juvenile breasts, and 43.8 per cent had pendulous mammae.

Forty-five per cent of the dementia precox subjects showed normal brains both macroscopically and microscopically, but 30 per cent had what appeared thinner meninges than normal, while 20 per cent had thicker than normal. The average brain weight of the schizophrenics between 20 and 30 was 1140.5 grams as compared to 982.5 grams for the non-dementia precox cases; 30 to 40 years, 1231.75 grams as compared to 1174.83 grams; 40 to 50 years, 1196.33 to 1063.4 grams; 50 to 60 years, 1187.5 to 1146.93 grams; 60 to 70 years, 1153 to 1104.25 grams; and over 70 years, 1023 grams as compared to 1131.97 grams.

In the dementia precox group, 37.5 per cent showed a normal hypophysis, 43.7 per cent an atrophic or fibrosed hypophysis, and 18.8 per cent acute congestion. This gland in the 20 to 30 years old schizophrenic group showed an average weight of 805 mgm. as compared to 670 mgm. in the general group; 30 to 40 years, 662.5 mgm. as compared to 768.33 mgm.; 40 to 50 years, 806.67 mgm. as to 786 mgm.; 50 to 60 years, 816.67 mgm. as to 855 mgm.; 60 to 70 years, 680 mgm. as to 802.5 mgm.; and over 70 years, 657.67 mgm. as to 762.59 mgm. The cell content of the glands in the dementia precox cadavers showed an average of 52 per cent eosinophile cells, 21 per cent basophils, and 27 per cent neutrophils, with 29.4 per cent of the glands showing the relation 60-20-20; 17.7 per cent, 70-15-15, and a similar number, 30-10-60; and 15 per cent showing 30-30-40, as compared to the glands found in the non-dementia precox group, which showed an average of 57 per cent eosinophils, 20 per cent basophils, and 23 per cent neutrophils. Of these glands 29.4 per cent showed the relation 70-10-20; 17.7 per cent, 60-20-20; 15 per cent, 50-20-30; and a similar number, 40-50-10.

The pineal gland was normal in 46 per cent of the dementia precox group, and 38 per cent showed sclerosis.

The thymus glands from the dementia precox cadavers showed anything from 0 to 100 per cent active tissue, but only 20 per cent showed more than 25 per cent or more activity, while 57 per cent of the glands showed 5 per cent or less active

tissue present. This gland from the catatonics between 20 and 30 years of age on the average weighed 5 grams, and showed 20 per cent active tissue; from the hebephrenics, 1.2 grams and 70 per cent; while the mixed group showed 9.73 grams and 3 per cent, with an average of 6.73 grams and 24 per cent, as compared to the control cases, 7.33 grams and 63.3 per cent. The 30 to 40 year group showed 6.4 grams without active tissue; 5.9 grams with 5 per cent, and 4 grams without activity, respectively catatonic, hebephrenic, and mixed, with an average of 5.55 grams and 5 per cent, as compared to 12.11 grams and 39.33 per cent active tissue in the control group. From 40 to 50 years all of the dementia precox cases showed an average of 6.02 grams and 55 per cent as compared to 10 grams and 16.6 per cent in the others; from 50 to 60 years, 7.1 grams and 7 per cent as to 9.1 grams and 19.9 per cent; from 60 to 70 years, 16.1 grams and 0.5 per cent as to 12.25 grams and 1.5 per cent; and over 70 years, 6.62 grams and 2.4 per cent as compared to 9.48 grams and 2.14 per cent active tissue.

Forty per cent of the thyroids from the dementia precox cadavers were normal, 35 per cent were atrophic, 15 per cent showed thyroiditis, and 10 per cent were hypertrophied. The 20 to 30 group of catatonics showed an average weight for the thyroid of 13.15 grams, the hebephrenics 21.5 grams, the mixed 18.27 grams, with an average for the dementia precox cases of 17.27 grams, as compared to the control weight of 24.79 grams. From 30 to 40 years the weights were 18, 16.62, and 28.7 grams, with an average of 19.99 grams, as compared to 18.05; 40 to 50 years, 25.5 grams, and 25.85 grams for the catatonics and hebephrenics, respectively, with an average of 25.6 grams, compared to 18.18; 50 to 60 years showed an average for the dementia precox cases of 21.37 grams as compared to 23.17 grams; 60 to 70 years, 18.25 grams against 19.55 grams; and over 70 years 25.63 grams, compared to 19.65 grams.

The parathyroids in the dementia precox cases showed 40 per cent of the glands with marked fatty infiltration, 26.6 per cent atrophy or sclerosis, 6.6 per cent increase of the interstitial cells, 13.5 per cent congestion, while only 13.3 per cent of the glands were normal.

The pancreas was normal in 30 per cent of the cases; 50 per cent showed fatty infiltration and degenerative changes, and 20 per cent were diagnosed pancreatitis. Many of the pathological changes were probably due to acute toxic or autolytic catabolism.

Both the cortex and medulla of the adrenals were normal in only one case, a woman 39 years of age with the catatonic type of dementia precox. She weighed 35 kgms. and was 162 cm. in height. Ten per cent of the cases showed normal medullas and 5.3 per cent enlarged medullas. Forty-two per cent showed degenerative changes in the whole gland, 5.3 per cent, fatty infiltration; 10.5 per cent, cloudy swelling; 42 per cent, markedly narrow cortex; 10.5 per cent, hypertrophied cortex, and 5.3 per cent, edema of the cortex. The catatonics from 20 to 30 years of age showed an average weight of 6.75 grams and 7.35 grams, respectively, for the right and left glands; the hebephrenics, 7.8 and 7.5; the mixed, 6.2 and 6.13, with an average of 6.67 and 6.77 grams, as compared to 5.3 and 6.86 grams for the control group; from 30 to 40 years, 5.5 and 5, 5.65 and 7.05, 6.5 and 7.2, and an average of 5.83 and 6.58, as compared to 6.02 and 5.83 grams; from 40 to 50 years, 5.47 and 6.37, as compared to 5.18 and 6.26; from 50 to 60 years, 6.38 and 6.18, as compared to 6.91 and 7.77; from 60 to 70 years, 5.23 and 5.1, as to 6.37 and 7.51; over 70 years, 5.15 and 4.53, as to 5.79 and 6.24 grams.

The uterus was normal in only 15 per cent of the cases, while none of the ovaries were normal. Twenty-five per cent of the subjects had had their ovaries previously removed, while of the ovaries examined, 33.3 per cent were atrophic, 60 per cent were sclerotic or cystic, and 6.3 per cent were cancerous. In the various age groups of control cases there were some changes in the ovaries, but nothing comparable to the general subnormality of the dementia precox gonads. From 20 to 30 years the average weight of the right and left ovaries was, respectively, 2.63 and 2.61 grams, as compared to 3.45 and 3.26 grams in the control cases, with only 25 per cent showing fibrosis; from 30 to 40 years, 3.4 and 4.2 grams as to 3.42 and 3.9 grams, with 20 per cent showing fibrosis and 20 per cent more showing other regressive changes; 40 to 50 years, 2.65 and 3.7 grams as to 3.51 and 3.26 grams, with 40 per cent showing atrophic changes; 50 to 60 years, 1.77 and 1.6 grams as to 6.42 and 4.15 grams, with 50 per cent showing atrophy, fibrosis, or cyst formation; 60 to 70 years, 1.4 and 1.45 grams as to 1.98 and 1.87 grams, with 42 per cent atrophic; and over 70 years of age, 1.87 and 1.7 grams as to 2.41 and 2.61 grams, with 58 per cent atrophic or sclerotic, and the remaining 42 per cent showing the normal regressive senile changes.

## DISCUSSION

Dementia precox in the past has been more or less placed in the class of incurable and hopeless diseases, and anything that offers a possible amelioration is worthy of support. Much suggestive work on the problem has been done in the past, but without proper cooperation and without being brought to a satisfactory conclusion.

The clinical and histo-pathological work that has already been completed shows that there is apparently no constant alteration in the brain substance, but a very consistent lack of gonadal incretion. Examination of eunuchs shows them to have schizophrenic characteristics with marked affect disorganization, while, on the other hand, unmistakable subjects of dementia precox are quite consistently eunuchoid in physique.

The castrated man or woman tends more or less towards a common type, that is, a juvenile form common to both sexes, or to a form in which, as in the intrauterine stage, sexual divergence has not yet taken place. In the ontogenetic development of the soma there is an asexual stage. The asexuality that for various reasons apparently develops to form the dementia precox symptom-complex is a very logical explanation for the familiar regression found in dementia precox.

It is well known that the endocrines are very sensitive to toxins, such as those of mumps and scarlet fever, as well as alcohol or opium, causing ovaritis or orchitis. There is abundant pathological evidence to show that patients dying in acute toxemia have hemorrhagic and destructive changes in the adrenals. Patients seldom recover from typhoid without some endocrine imbalance. Thus a history of toxemia or fatigue, either prenatal or postnatal, is suggestive as a precursor of dementia precox. The tenseness of catatonia might be explained by the apparent hyperfunction of the thyroid in these cases.

Without the driving force desired from the endocrines and, especially, the gonads, there is no wonder that the so-called dementia precox character develops.

If it be true that this disease is primarily a disorder of the endocrine system, and especially of the gonads, the supplying of this incretion should assist the individual in readjustment to life. It is hoped that in due time this will be proved.

## SUMMARY AND CONCLUSIONS

The literature, in general, supports the contention that endocrinopathy is consistently found in dementia precox cases.

Twenty-three eunuchs examined by me showed typical dementia precox or schizoid character—good intelligence and orientation, but distinct changes in the affect. Some retained sexual function but without libido.

Seventy living schizophrenic males examined showed at least 60 per cent to be eunuchoid in type and only 5.7 per cent having apparently nor-

mal testes, with also other signs of endocrine dysfunction. A large number functioned sexually.

Of forty living female subjects of dementia precox, 52.5 per cent had undoubted ovarian disease, although some had been able to be pregnant.

Pathological examination of 158 male and 24 female schizophrenics disclosed marked endocrine changes. No catatonic cadavers over 50 years of age were seen. No consistent pathological or biometric changes were found in the endocrines except in the gonads, although only a small percentage of the subjects had normal adrenals. The thyroid was consistently normal or hypertrophied in all cases of catatonic dementia precox. In the dementia precox cases no normal ovaries and only a small percentage of normal testes were found. The male dementia precox subjects of the catatonic type showed an average weight of 13.17 and 12.47 grams, respectively, for the right and left testes; the hebephrenic, 11.47 and 11.40 grams; and the mixed, 13.61 and 12.90 grams; with a general average for all the dementia precox males of 13.26 and 12.85 grams, as compared to 13.84 and 13.66 grams for the control psychotic group. The female dementia precox subjects showed an average weight of 3.6 and 3.3 grams, respectively, for the right and left ovaries, in the catatonics; 3.28 and 3.17 grams in the hebephrenics; 2.01 and 1.88 grams in the mixed group; with a general average of 2.96 and 2.75 grams, as compared to 3.28 and 2.85 grams for the control females.

Tuberculosis was the lethal disease in 39.9 per cent of the men but in only 15 per cent of the women. Myocardial degeneration was consistently present in a large percentage of both the male and female dementia precox cases, and pneumonia was a very frequent cause of death in both sexes. Almost every dementia precox individual gave a history of having had one or more of the severe toxemias. At least a fourth of the subjects had inherited defective somatoplasm.

This study as a whole indicates that dementia precox is primarily an endocrinopathy in which the gonads are consistently degenerated or hypo-functioning.

Sexual activity and fecundity are no adequate criteria of gonad increment, but rather the state of the interstitial lipid should be taken as the criterion of normality.

Supplying of the endocrine deficiency should assist in the social adjustment of the victims of dementia precox.

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# THE ORAL ADMINISTRATION OF ADRENALIN

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That adrenalin is ineffective when administered by mouth seems to be an accepted fact. That it is destroyed by the gastric and intestinal juice is the general belief. Systemic effects from oral administration are thus questionable.

Menninger (1927) states that only large doses of adrenalin, when given by mouth, have any effects on the blood pressure of experimental animals. He quotes Herter and Wakeman (1902) as attributing no effects, when adrenalin was given in "ordinary" doses. No effects were produced in a well-fed dog weighing 13 kgm. when 10 cc. of 1-1000 was administered. A one per cent glycosuria was produced in a dog, over a short period of time, without other symptoms, when 30 cc. of 1-1000 was given. Falta and Ivacovic (1909) found that even 20 mgm. or more per day did not produce any special manifestations in dogs.

Dorlencourt, Trias, and Paychere (1922) obtained only hyperglycemia and never any changes in blood pressure. They administered large doses and concluded from their results that adrenalin passes through the portal system to the liver, where it is destroyed. They used chloralose as an anesthetic, under the assumption (warranted by the results of their own observations) that it would not increase the blood sugar.

After reviewing clinical and other observations, Menninger (1927) comes to the conclusion that the results are inconsistent and unreliable. It was therefore suggested to us by Professor T. C. Burnett that the experiments should be repeated without anesthesia, thus eliminating the possibility of hyperglycemia from the chloralose.

## EXPERIMENTAL

1. *The effects of adrenalin on the blood sugar of dogs, when administered by stomach tube.*

Only dogs in the post-absorptive state were used. The animals were trained to remain quiet throughout the experiments, while strapped to a dog board, with the stomach tube in place. Blood was drawn from the femoral artery. A normal sample was taken and 10 cc. of 1-1000 adrenalin in 40 cc. of water administered by stomach tube and washed down with 10 cc. of water. Immediately following the administration of adrenalin another sample of blood was drawn in order to check up any possible

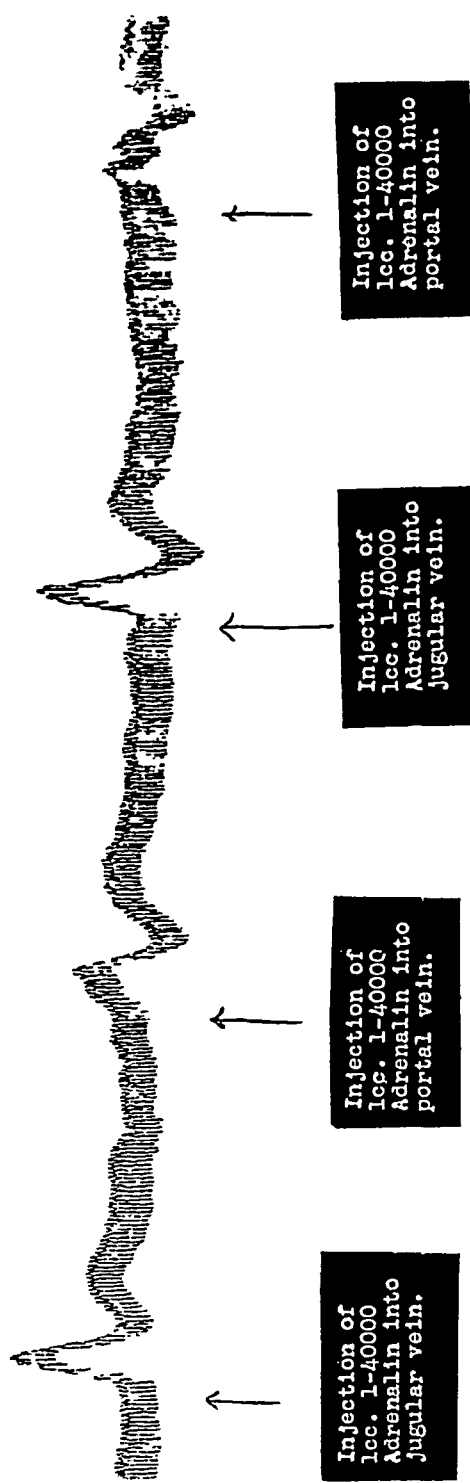
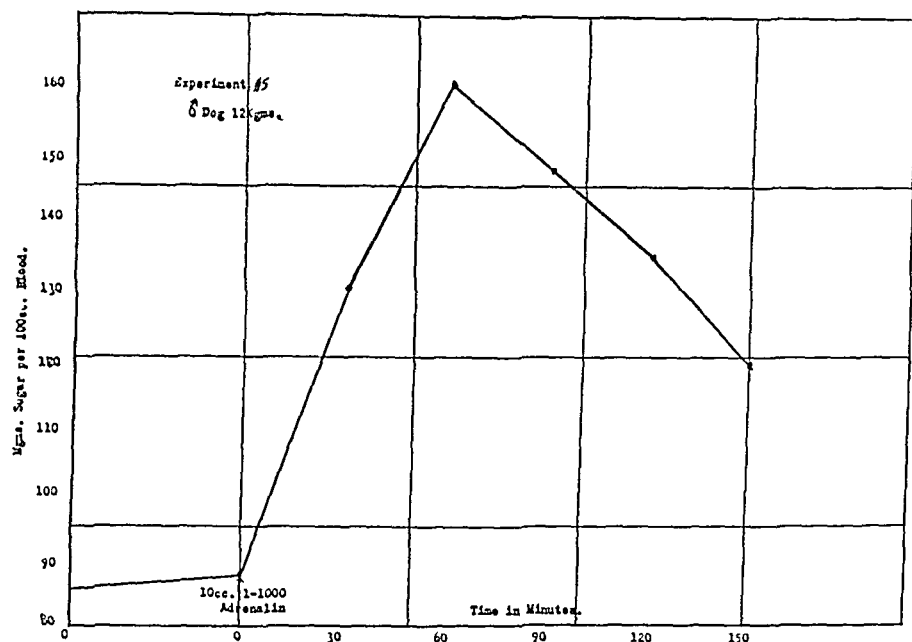


Fig. 1. Injection of 1cc. 1-40,000 Adrenalin into jugular vein followed by a similar injection into portal vein.

## ORAL ADMINISTRATION OF ADRENALIN



Animal	Before Administration of Adrenalin	Immediately Following Adrenalin	Time in Minutes After Administration of Adrenalin				
			30	60	90	120	150
1 10 kgm. control	mgm. 96 1	mgm. 95 2	mgm. 97	mgm. 97 5	mgm. 98	mgm. 98	mgm. 95
2 10 kgm.	99	101	130	151	135	123	118
3 10 kgm.	96	95 6	128	165		137	129
4 12 kgm. control	86	88 2	85	87	87	86 5	88
5 12 kgm.	86	87 3	130	160	148	132	119
6 12 kgm.	87 5	85	132	161	147	130	117
7 14 kgm.	103	103	126	148	137	125	120
8 14 kgm.	105	107	135	170	160	130	121
9 11 kgm. control	100 5	103	107	106	106	104	102
10 11 kgm.	100	100	160	160	136	118	
11 15 kgm.	104	105 5		171	158	131 5	121
12 15 kgm.	101	104	133	159	142	130	

changes due to handling. Samples of blood were drawn every half hour, over a period of from  $2\frac{1}{2}$  to 3 hours.

Control experiments were performed by administering 50 cc. of water, instead of adrenalin. The animals were subjected to the least possible amount of handling. All the controls showed a constant blood sugar level throughout the experiments. Neither the experimental method nor the administration of water gave any rise in the blood sugar.

The accompanying typical curve shows that the first noticeable effect after the oral administration of adrenalin appears after one-half hour and the blood sugar rises considerably by the end of the first hour; it remains above the normal level for more than  $2\frac{1}{2}$  hours. Outside of the blood sugar changes, the animals showed no signs of distress nor manifestations of the action of adrenalin. When administered by stomach tube, adrenalin showed no effect on the blood pressure.

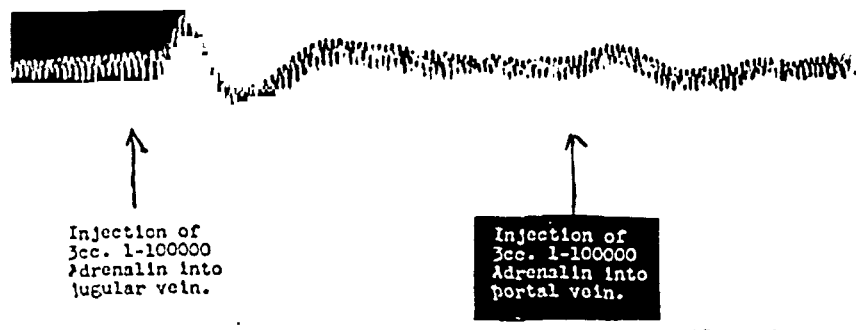


Fig. 2. Injection of 3cc. 1-100,000 Adrenalin into Jugular vein followed by a similar injection into portal vein.

## 2. Injection of Adrenalin.

The dogs were anesthetized with ether, using the drop method. As soon as the animals were under, the femoral arteries in both legs were exposed; next the jugular on the left side, and finally the abdomen was opened by means of a median longitudinal incision, sufficiently large to permit access to the portal veins, vena cava, and the liver.

The exposed parts were kept covered with absorbent cotton soaked with warm Locke's solution. The abdomen was covered with towels moistened in Locke's solution, and kept warm by a 200-watt light over the operating table. After the animal was completely prepared, the blood pressure apparatus was connected to one of the femoral arteries.

Adrenalin was injected into the jugular, vena cava, portal vein, and the liver. Care was taken to time each injection with a stop watch in order to insure uniformity. Injections of 3 cc. of 1-100,000 were made first into the jugular and followed by an equivalent injection into the portal, and vice-versa. In order to reduce the volume of the injections, 1 cc. of 1-40,000 were also tried on the same animals.

The accompanying records show that the rise in blood pressure, following injection of 3 cc. of 1-100,000 into the portal vein, was just perceptible. When 1 cc. of 1-40,000 was injected into the portal vein, the rise in blood pressure was slightly more pronounced, but still considerably less than that due to similar injections into the jugular. Injections into the vena cava or the jugular always showed greater effects on the blood pressure than injections into the portal vein, or into the liver. Further work is in progress to determine the exact location of the removal of the pressor action of adrenalin when given orally.

#### SUMMARY AND CONCLUSIONS

1. Adrenalin was administered by stomach tube to 12 dogs. It caused a rise in the blood sugar level.
2. Adrenalin is absorbed, therefore, through the gastro-enteric tract, other than the mouth and throat.
3. None of the other usually apparent effects of adrenalin were noted.
4. The blood pressure was not affected.
5. Injections of adrenalin into the jugular and the vena cava gave materially greater rises in blood pressure than did equivalent injections into the portal vein or into the liver.
6. Apparently the liver removes most of the pressor effect of adrenalin.
7. It appears that the liver is able to remove the pressor effect of adrenalin as fast as the drug is absorbed, when administered by stomach tube.

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## INFRA-RED STERILITY: PRELIMINARY REPORT

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Recent work (1) has shown that sterility can be produced in males by the application of heat to the testes. Snyder (2) ascribes the sterilizing effect of x-rays in rats to the heating effect. Recently Zalewski and Trifonoff (3) have reported that the local application of infra-red rays to the testes may be of benefit in clinical gonad insufficiency. This might be due secondarily to destructive effects on the spermatogenic tissue leading to better nutrition of the interstitial cells.

We have studied the sterilizing effect of infra-red rays in rats using both mating tests and histological study of the glands as criteria of the effects in the testes. Complementary studies have been made using heated air as the sterilizing agent.

Some preliminary experiments were made in March, 1927, two males being treated with infra-red rays. The apparatus for treatment consisted of a wooden box containing an infra-red burner. Directly above this burner a hole  $2\frac{1}{2} \times 1\frac{1}{2}$  inches was cut, which allowed the superimposed testes to be directly exposed to the rays. A fairly constant temperature of  $48^{\circ}\text{C}.$ , varying no more than half a degree at the aperture, was obtained by this apparatus. Rats that have been handled frequently do not seem to mind the treatment and they may be held in position by the tail.

After a treatment of five minutes, each male was penned with two females. Each was found to be fertile up to about fifty-four days after treatment, when they became sterile for a period of a month. After this they were again fertile. Vaginal smears taken after copulation during the latter part of the sterile period showed no living spermatozoa present. Sterility produced by this means evidently does not produce senility. The mating instincts are at no time lost. This fact has been previously observed by Young (l. c.) in his work with guinea pigs.

It seemed desirable to determine whether the sterility produced in this experiment was due to some inherent ray in the infra-red or whether the results were traceable to thermal factors. To determine this point another series of experiments was begun in November. Four checked males were treated for five minutes with infra-red rays in the manner previously described. Four other males were similarly treated for five minutes at  $48^{\circ}\text{C}.$ , but with air heated by a steam boiler. The males were then mated.

The mating tests, while indicating the existence of sterility, do not very sharply define its beginning or ending unless a rather large number of females having various oestrus cycles are penned with a single male.

Our facilities did not permit the penning of more than two females with a male, hence the indicated periods at which sterility begins and ends are quite variable.

Nevertheless, it was shown that there is a definite sterility period which is in turn followed by a fertility period, as the following data, based upon breeding tests, indicate:

Heated Air Treatment		
Rats	Sterility Begins— Days after Treatment	Sterility Ends— Days after Treatment
No. 93	16	41
No. 94	24	53
No. 95	24	61
No. 96	27	82

Infra-Red Treatment		
No. 97	Not determined	47
No. 98	38	85
No. 99	34	65
No. 100	Not determined	84

Young checked his sterility work with guinea pigs by histological study. He found that germinal degeneration took place in a rather definite order. "Large primary spermatocytes, secondary spermatocytes, young spermatids, a few spermatogonia are affected first. Subsequently, the older spermatids, spermatozoa within the seminiferous tubules and the early growth stages of the primary spermatocytes are affected." The epididymal sperm seems to be protected but the sperm in the distal and proximal ends undergo degeneration and disappear, apparently by liquifaction.

Snyder does not give a thorough account of his histological studies; however, during the sterility period he failed to observe any active stages of spermatogenesis. Upon his observations he concluded that the roentgen rays affect the actively growing tissue more than quiescent tissue; spermatozoa and young spermatogonia are most resistive.

Studies of degeneration in the testis were made upon two male rats treated for fifteen minutes with heated air and two others treated with infra-red rays for the same length of time. These rats had been previously checked in the usual manner and found to be fertile before treatment. Rat No. 1 (heated air) and No. 3 (infra-red) were castrated unilaterally on the seventh day, the left testis being removed. On the fourteenth day rats No. 2 (heated air) and No. 4 (infra-red) were castrated in the same manner except the right testis was removed. On the twenty-first day rats Nos. 1 and 3 and on the twenty-eighth day Nos. 2 and 4 were killed and the remaining testes taken.

The tissues were killed in Bouin's fluid, imbedded in paraffin and sectioned at 8 microns. They were stained with Gentian violet. The



epididymus and the vas deferens were sectioned also. In order to study the distribution of degenerative changes sections were taken at short distances apart throughout the entire testis. A normal testis prepared in a similar manner was used for comparison.

As nearly as possible the following chart indicates the comparative observations of the tissue.

## HEATED AIR SERIES

	7 Days	14 Days	21 Days	28 Days
Sperm in seminiferous tubules.	Many normal sperm, quite a few degenerated to some extent.	As many sperm present as in 7-day, but more degenerated ones and degenerated to a greater degree.	A very few normal sperm. Also a few degenerated ones.	More normal sperm and spermatids. Most tubules regenerated to great extent, some still degenerate.
Sperm in ducts.	Most ducts very full of normal sperm. A few small ducts with none.	Not as many sperm present. No noticeable degeneration.	Still fewer sperm present. Quite a few have degenerated.	Most tubules in same condition as in 21 days. Many degenerate sperm. Some tubes in which all sperm are degenerate.
Nuclear figures.	General degeneration. Half tubules show decided degeneration of chromatin. A few tubules almost empty. Only a nuclear figure here and there.	Slight regeneration, a few more nuclear figures.	Some tubules still badly degenerated; more apparent regeneration with many nuclear figures.	General regeneration with many nuclear figures present. A few tubules still in bad condition.

## INFRA-RED SERIES

	7 Days	14 Days	21 Days	28 Days
Sperm in seminiferous tubules.	Many normal sperm, a few degenerated ones.	Numerous sperm still present, but many degenerated ones.	Few normal sperm. Many degenerated heads and tails.	Practically no sperm; some degenerated heads and tails.
Sperm and ducts.	Tubules full of normal sperm.	About as many sperm in ducts, but a few are empty, and some sperms are quite degenerate.	Only one-half as many as in 14-day; a lot of degenerated sperm, several tubules empty.	No normal sperm. Very few chromatin dots in center of few of ducts.
Nuclear figures.	Degenerate chromatin in half of the tubules; general cell condition slightly different from steam heat of same age; few nuclear figures.	Numerous nuclear figures. Regeneration quite evident in most tubules, but some still degenerate.	Many nuclear figures. A few tubules still quite degenerate.	Many more nuclear figures. Activity of cells next to the tubule wall quite evident.

In order to see if it were possible to establish a second sterility period, two males from each set were given a second treatment for the same length of time. This was given thirty-five days after the first treatment. A second sterility period occurs in animals treated in this manner, as is shown by the following table.

## INFRA-RED STERILITY

## Single Hot Air Treatment

Rat	Days after Treatment		Days after Treatment	
	First Sterility Begins	Ends	Second Sterility Begins	Ends
No. 96	24	53	75	102
No. 94	27	82	103	145

## Infra-Red Treatment

Rat	Days after Treatment		Days after Treatment	
	First Sterility Begins	Ends	Second Sterility Begins	Ends
No. 98	Undetermined	47	77	Undetermined
No. 97	38	65	92	113

In this experiment the second sterility period seems to be due to the second treatment. However, in the animals treated but once it was observed that a second sterility period occurred which, to all appearances, was similar to that of the animals treated twice.

The following table may be compared with the previous one.

## Single Hot Air Treatment

Rat	Days after Treatment		Days after Treatment	
	First Sterility Begins	Ends	Second Sterility Begins	Ends
No. 93	16	41	60	97
No. 95	24	61	80	102

## Infra-Red Treatment

Rat	Days after Treatment		Days after Treatment	
	First Sterility Begins	Ends	Second Sterility Begins	Ends
No. 99	34	65	86	
No. 100		84	109	

It is quite evident that there is a general similarity in the effects produced by infra-red and heated air. However, since there are so many individual differences which play a great part, many more animals should be used; in fact, we are continuing the work at present with considerably larger numbers.

(Since the above was written 37 additional animals have been treated, all but one of which have become sterile.)

## SUMMARY.

Since sterility can be produced by hot air and infra-red rays, it seems reasonable to conclude that the causal factor in the infra-red is thermal.

This work confirms the work of Young, Snyder and several others, and adds a new agent for sterilization—one that can be administered with the minimum inconvenience and danger.

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## Abstract Department

Malignant tumors of the adrenal in children with report of a case. Bendixen, P. A. and F. H. Lamb, J. Lab. & Clin. Med. 12: 132. 1926.

A brief review of the literature on the subject with report of a case occurring in a girl, 5 years old. Suprarenal medullary malignancy is not an altogether unusual occurrence. In the majority of cases an orbital hemorrhage is the first sign observed, and it may occur before any tumor is palpable. The orbit first involved is often on the same side as the primary tumor, although the case reported was an exception. Diagnosis should not be difficult, once the orbital hemorrhage has occurred. The disease is likely to be mistaken for trauma, chloroma and scurvy. Surgical interference can be of no avail except as a palliative to drain a pyonephrosis or to meet other complications, as the metastases occur usually before a diagnosis can be made. Metastases probably occur through the lymph stream. The malignancy rarely metastasizes to the skin. The medulla of the suprarenal gland being neuroectodermic in origin, these malignant tumors are similar in their histological structure to malignant neoplasms of the sympathetic nervous system, and they are correctly designated as neuroblastoma.—I. B.

Hemorrhage of the suprarenals in the new born infant. Goldzieher, M. A. and H. M. Greenwald, Am. J. Dis. Child. 36: 324. 1928.

Suprarenal hemorrhage in the new born infant can be diagnosed from its symptoms, such as sudden onset of temperature and rapid breathing and occasionally by the presence of a palpable tumor in the abdomen or by punctiform hemorrhages of the skin or mucous membranes. Exsanguination or intestinal obstruction may justify surgical intervention, otherwise, patients with the symptoms of acute cortical insufficiency should be treated by the continued administration of the cortical hormone. Two cases are reported in which adrenal hemorrhage was diagnosed; one came to autopsy and the other recovered.—M. B. G.

Experiments on the function of the interrenal organs of selachians (Untersuchungen über die Funktion des Interrenalorgans der Selachier). Kisch, B., Arch. f. d. ges. Physiol, 219: 426. 1928.

Complete removal of the interrenal gland from selachians leads rapidly to death. Sham-operated animals lived three or four times as long. The gland in *Torpedo ocellata* is two or three times as great as that in *T. marmorata* of the same weight. The latter survive the operation two or three times as long. Following the extirpation a persistent paling of the pigment of the skin chromatophores, whereby the animals take on a dirty-gray color, slowing of breathing, muscle weakness, shortening of the body musculature, hypersensitivity to oxygen scarcity, and early death, which often suddenly follows intensive muscular activity, occurs. Hence the symptoms of adynamia, respiratory disturbance, increased sensitivity to oxygen failure and sudden death after intense muscular activity, which follow adrenalectomy in mammals, must be attributed to removal of the adrenal cortex. It is considered that the interrenal tissue (the adrenal cortex in mammals) gives to the circulation some compound which favors the oxidative decomposition of definite metabolic products, which in excess have a toxic action leading to the above mentioned symptoms and finally to death. Anything increasing the concentration of these products, such as muscular activity, lowering of oxygen concentration, loss of blood, must increase the symptoms and accelerate death. Injection of acid extracts of interrenal tissue may delay the symptoms in selachians for hours. Injections of sea-water, adrenine, or liver extract, have no such effect.—A. T. C.

The amount of adrenin in the adrenal glands in total starvation (Sur la teneur en adrenaline des capsule surrenales dans l'inanition totale). Mouriquand, G. and A. Leulier, Compt. rend. Soc. de biol. 99: 280. 1928.

In guinea pigs kept five days without food, but given water, the adrenals showed an increase in both the free and total adrenin.—J. C. D.

**The effect of subcutaneously injected epinephrin in normal human subjects.** Koppanyi, T., *Proc. Soc. Exper. Biol. & Med.* 25: 744. 1928.

Six young, healthy medical students were subjected to subcutaneous epinephrin injections (0.4 cc. of a 1:1000 solution). Before injection the normal systolic and diastolic blood pressure and the heart and respiratory rates were determined. From 10 to 15 minutes following the injection of epinephrin there was a rise in blood pressure of 30 to 50 mm. of Hg., a slight increase in the heart and respiratory rates without any massage. The injected area was blanched, the face pale, there was a slight muscular twitching in the arms and legs, and a thumping, palpitating heart was evident. The subjects felt slight headache, throbbing in the head, some nausea, the mouth was dry, and there was in some cases subjective sensation of warmth; in others, the hands and feet felt cold. Nervousness and general feeling of anxiety were evident in most subjects, whereas one subject appeared to be in a fighting mood. The injected areas were massaged from 15 minutes to 48 hours following injections. In the course of the 48 hours, the area was massaged about 25 times. On the whole, all symptoms which appeared following epinephrin injection without massage, could be duplicated by massaging the injected area, for about 48 hours. They were, however, much less marked, the blood pressure rises, for instance, being seldom more than from 7 to 15 mm. of Hg. The rise was practically the same when one massaged the area 20 minutes or 20 hours following the injection. One subject developed constipation following the injection.—Author's Abst. (abbreviated).

**Suprarenal apoplexy, bilateral.** Pearl, F. V. and H. Brunn, *Surg. Gynec. Obst.* 47: 393. 1928.

A case of bilateral suprarenal apoplexy of the adrenals in a man aged 45 years is described. The literature is reviewed. At postmortem this case showed almost complete destruction of adrenal tissue.—A. T. C.

**The influence of the adrenals on the urea-formation and barrier-function of the liver** (Ueber den Einfluss der Nebennieren auf die harnstoffbildende und Barrierefunktion der Leber). Putschkow, N. W. and W. W. Krassnow, *Arch. f. d. ges. Physiol.* 220: 44. 1928.

Amino-acid and amino nitrogen increases in the blood and urine following adrenal extirpation, while at the same time there is a sudden decrease in urea content. These findings indicate cessation of liver function and correspond to those following liver extirpation. The isolated liver of adrenalectomized animals acts on ammonium salts and biogenous amines more feebly than the normal liver. Extract of adrenals restores the barrier function of the liver to normal. The active principle of the adrenals is extraordinarily labile and decomposes in 15 to 20 minutes. It is not adrenin and is absent from other body organs.—A. T. C.

**A study of the pigment in Addison's disease.** Spohr, C. and R. A. Moore, *J. Lab. & Clin. Med.* 12: 438. 1927.

The ultimate chemical analysis of a pigment derived from the lymph glands in a case of Addison's disease is reported. The evidence seems to point that this pigment is a melanin and the absence of any other explainable cause of the melaninosis than the Addison's disease would lead one to believe that there was more than a casual relationship between the two. The authors believe the pigment laid down in the tissues to be melanin, and that it bears a direct relationship to the condition responsible for the pathologic complex of Addison's disease.—I. B.

**New clinical and experimental studies of the inter-relations of the thyroid, adrenals and the nervous system.** Crile, G. W., *New England J. Med.* 198: 988. 1928.

The crises of hyperthyroidism are due to the interaction of the thyroid and adrenal medulla. Thyroid extract after a latent period increases the electric conductivity and capacity of the organs and tissues in the body. Adrenin has an immediate effect. It raises the conductivity, temperature, and capacity of nervous tissue and the adrenal medulla, while it has the opposite effect on the other tissues. This, it would seem, increases the difference in potential between

the different tissues. "It would appear from the finding (the increased conductivity and capacity of the medulla after adrenin injections) that the medulla of the adrenal functions as nerve tissue; perhaps it is the brain of the vegetative system, its probable function being to charge up—to energize the vegetative system." On this theory, four cases of hyperthyroidism were treated by a hemi-adrenalectomy with very encouraging results.—J. C. D.

**Action of ephedrin on intestine and bronchi.** Halsey, J. T., *Proc. Soc. Exper. Biol. & Med.* 20: 16. 1928.

In more than 100 experiments, no evidence of a depressant action of ephedrin on the isolated rabbit intestine was found.—M. O. L.

**Experimental histology and clinical observations on the destruction by chemical means of the sympathetic of the spermatic cord** (*Observaciones experimentales histológicas y clínicas sobre la simpatectomía química del cordón espermática*). Cassuto, A., *Rev. Sud-Am. de endocrinol.* 11: 221. 1928. *Abst., Physiol. Absts.* 13: 319.

It is claimed that painting the internal spermatic artery to the vas deferens with a 5 per cent solution of phenol destroys the sympathetic nerves to these vessels, thereby causing increased blood flow to the testicles. This is followed in men and dogs by increased spermatogenesis and return of sexual potency.

**Ripe follicles are not essential for the appearance of the oestrous** (*La présence du follicule mur n'est pas indispensable à l'apparition de l'oestrous*). Courrier, R., *Compt. rend. Soc. de biol.* 99: 26. 1928.

In the bat, the early stages of oestrous appear normally in the absence of ripe follicles.—J. C. D.

**Does the follicular hormone inhibit that of the corpus luteum?** (*L'hormone folliculaire inhibe-t-elle l'hormone lutéinique?*). Courrier, R., *Compt. rend. Soc. de biol.* 99: 224. 1928.

Rabbits, five days after mating, were injected with follicular hormone, twice daily for six days. On autopsy, there were no corpora lutea, no pregnancies and the endometrium was of the normal type.—J. C. D.

**Relations between the hormone of the corpus luteum and of the follicle** (*Les rapports qui existent entre les hormones folliculaire et lutéinique*).

**Follicular hormone cannot replace that of the corpus luteum** (*La folliculine ne peut suppléer l'hormone lutéinique*). Courrier, R. and M. Masse, *Compt. rend. Soc. de biol.* 99: 263; 265. 1928.

Five days after mating, rabbits were spayed and then given regular injections of follicular hormone in varied doses. Under these conditions, implantation does not take place. Histological study of the uterus shows that while folliculin can maintain the uterine mucosa in an advanced state of preparation for implantation, it cannot cause the final changes, which take place when the corpus luteum is present. Folliculine does, however, have a marked action in developing the uterine smooth muscle. These experiments support the theory of the double nature of the ovarian hormones.—J. C. D.

**The female sex hormone, clinical experiences with various ovarian preparations.** (No title given in the original German report.) Fraenkel, L., *Therap. d. Gegenw.* 68: 524. 1927.

The female sex hormone is found in the ovarian follicle, corpus luteum, decidua, placenta, blood and milk, but not in the cerebro-spinal fluid. With extracts made from corpora lutea the writer was able to allay deficiency disturbances, but did not succeed in stimulating menstruation. The preparations were effective when given by mouth, but the dosage had to be 20 times the subcutaneous dose because of partial destruction in the gastro-intestinal tract. The writer is very skeptical about the corpus luteum containing a stimulating substance (Agomensin) and an inhibiting substance (Sistomensin). The author treated 114 subjects who had been carefully selected because of the following indications: amenorrhea, splasia of the uterus and genitalia; infantilism, secondary atrophy following surgical or x-ray castration; and endocrine disturb-

cows. If one reckons that 1 unit is represented by 0.001 mgm. of solids then 1 gram of the hormone can be obtained from 200 liters of urine. The female sex hormone dialyzes readily through various kinds of membranes. It dialyzes more quickly than many other constituents of the urine. The preparation of the hormone from urine is easier than from placenta or follicular fluid which has a high protein content. The method of preparation may be the same but a slight modification is desirable. (1) The filtered urine is extracted with some lipoid solvent, other than alcohol, to eliminate urea. (2) The extract is treated with hot alkali, taken up in water and shaken with ether. (3) The ether soluble part is taken up in distilled water or weak acetic acid heated and filtered. The hormone is contained in the filtrate which is water-clear, bright and free from color and odor. The total solids are only 0.01 to 0.001 mgm. per Mouse Unit.—E. P. Bugbee.

**The heart hormone (Ueber das Herz hormon).** Rigler, R. and R. Singer, Arch. f. d. ges. Physiol. 220: 56. 1928.

The specificity of Haberlandt's "hormone" is denied. It is not a hormone in the strict sense of the word.—A. T. C.

**Hypodynamic heart condition and the "heart hormone" (Hypodynamischer Herz Zustand und "Herzhormon").** Teitel-Bernard, A., Arch. f. d. ges. Physiol. 220: 212. 1928.

The activity of hypodynamic hearts can be increased by forcing in air or by other mechanical means of enlargement, whereby active substances are pressed out of the heart musculature. These are not identical with Loewi's accelerating substance, and are not hormones.—A. T. C.

**Is there an antagonism between the water soluble extract of anterior lobe and folliculine? (Existe-t-il un antagonisme entre l'extrait hydrosoluble du lobe antérieur de l'hypophyse et la folliculine?)** Brouha, L., Compt. rend. soc. de biol. 99: 43. 1928.

If rats are injected simultaneously with both these substances, the usual effects of folliculine are evident: the precocious sexual development and normal oestrous cycle. The pituitary extract acts, therefore, through its rapid alteration of the corpora lutea with the resulting suppression of the follicular hormone and not by direct antagonism to it.—J. C. D.

**The action on diabetes insipidus of powdered posterior lobe of hypophysis (Action de la poudre de lobe postérieur d'hypophyse sur le diabète insipide).** Choay, A. and L. Choay, Compt. rend. Soc. de biol. 99: 359. 1928.

Powder from beef glands dried in the cold in vacuo is snuffed up into the nose like snuff. Four doses per day, of from 20 to 50 mgm. each, were used in an adult passing 15 liters of urine. His output fell to 3 liters. Where the output is over 20 liters, this method can be used only to supplement the usual injections of hypophysis. In 12 less severe cases it has proved successful over a period of five years.—J. C. D.

**The various morphological alterations of the rhinopharynx in relation to the hypophysal syndrome (De quelques altérations morphologiques rhinopharyngées en relation avec le syndrome hypophysaire).** Curchod, E., Schweiz. med. Wchnschr. 58: 537. 1928.

The author emphasizes the fact that the epithelial portion of the pituitary is developed from the ectodermal pharyngeal pouch. For this reason the pituitary is related to the morphological development of the nose and nasal appendages. He describes a case of acromegaly in a woman 21 years of age, weight 65 kgm., height 65 inches. The nose was very broad throughout the transverse diameter. The turbinates were very large and there was a diffuse edematous infiltration of the nasal mucous membrane. The inferior turbinate was so large that it produced a complete obstruction of the anterior nares. Anatomical pathological examination revealed an angiomatous hyperplasia of the mucous membrane. The posterior pharynx had areas of hyperplastic lymphoid tissue. The lingual tonsils were very large. The pharyngeal tonsils were rather small, as they had been partially excised. X-ray of the skull showed a voluminous frontal sinus, the sella turcica was large but within normal limits. Thymus findings were negative. The muscular development

was good and the basal metabolism was 45% above normal. The anterior lobe of the pituitary influences the development and form of the nose as well as of the nasal appendages.—R. C. Moehlig.

**The mechanism of the influencing of blood sugar by pituitary extracts (Beiträge zum Mechanismus der Blutzuckerbeeinflussung durch Hypophysenextrakte).** Fritz, G., Arch. f. d. ges. Physiol. 220: 101. 1928.

Intramuscular injection of posterior pituitary extract causes increase of blood sugar in mammals. The action is secondary through mobilization of adrenin: it is not produced in adrenalectomized animals. The mobilization of adrenin results from general sympathetic stimulation.—A. T. C.

**Pituitary extract in pyelitis.** Miller, J. A., New York State J. Med. 28: 720. 1928.

The report is based upon the administration of pituitary extract in parturient and in non-pregnant women. In cases where pituitary extract was used pyelitis did not occur as a post partum complication. Where pyelitis occurred before delivery, the use of pituitary extract in inducing labor as a routine measure effected an immediate cure. The injection of pituitary extract, 1 cc. at intervals of 5 days for 3 injections, prevented the recurrence of pyelitis in chronic cases of non-pregnant pyelitis. Whether this cure is permanent or not remains to be seen. Pituitary extract has the effect of restoring the tonus of the ureter, increasing the contractility and preventing stasis of urine and resultant infection of the genito-urinary tract.—M. B. G.

**Histological evidence of colloid absorption directly by the blood-vessels of pars anterior of the human hypophysis.** Rasmussen, A. T., Quart. J. Exper. Physiol. 17: 149. 1927.

Histological examination of about a hundred apparently normal adult human hypophyses from cases of accidental death revealed colloid in the blood-vessels of only two specimens. In one of these, a young pregnant woman, it was abundant and could be seen in both the capsular veins of the anterior lobe, veins emerging from the region of the stalk, as well as in the sinusoids proper. The method by which the colloid globules get into the vascular channels is not evident. There are indications of degeneration in some of the cells surrounding the colloid in many of the small vesicles or pseudoacini in pars anterior, and the colloid may be separated from the interstitial tissue and blood channels by only very thin flattened cells, but conditions where the colloid is actually in the process of entering the sinusoids were not located even after diligent search in supposedly very favorable material.—Author's Summary.

**The weight of the principal components of the normal male adult human hypophysis cerebri.** Rasmussen, A. T., Am. J. Anat. 42: 1. 1928.

An attempt was made to supply more accurate data, including the more useful statistical constants, on the size of the main body of the hypophysis and its constituent parts, by applying the paper-weight method to serial sections of 111 selected normal male adult human hypophyses, twenty to twenty-six years of age, from cases of sudden and usually accidental death. The method used gives the fresh weight of the gland after dissecting off as much of the adherent connective tissue as possible and removing the stalk, which accounts for a somewhat lower average weight than is usually given for the organ as a whole. The average weight of the main body of the hypophysis, including a variable amount of connective tissue or capsule, is 570 mgm. The extreme values are 400 mgm. and 855 mgm. The frequency distribution of the weights is, in general, of the common fairly symmetrical unimodal type, except in the case of the colloid and parenchyma of pars intermedia, where it is greatly skewed in the positive direction. The variability, as expressed by the coefficient of variation, is highest in the case of pars intermedia (being around 90 or over, depending on whether or not the colloid is included); less in the posterior lobe (29); still less in the anterior lobe (21); and least in the gland as a whole (18). The anterior lobe decreases noticeably after fifty years of age. The coefficient of correlation ( $r$ ) between age and weight of the anterior lobe is  $-.293 \pm .059$ . The posterior lobe probably tends to increase slightly with age. As a result, there is a less marked decrease in the weight of the whole gland than in the anterior lobe. The parenchyma of pars intermedia

seems to increase distinctly with age, but when tested statistically the results are not significant, on account of the limited number of cases and the great individual variability. There is no evidence the colloid increases with age in the adult.—Author's Summary (Abbreviated).

**The hypophysis and the urinary excretion of inorganic phosphate, sulphate and chloride.** Tung, P. C., H. C. Chang and S. M. Ling, *Chinese J. Physiol.* 2: 231. 1928.

This investigation was made to test the validity of the claim that the excretion of urinary phosphate is readily abolished by the extirpation of the pituitary body or injury to the tuber cinereum, even though the phosphate content of the serum is not materially changed. Six dogs survived hypophysectomy from 1 to 16 days, and the excretion of phosphate was found to continue uninterruptedly. In five acute experiments a typical fall of urinary chlorides occurred after the operation. The phosphate output, however, first rose and then fell up to the fourth or fifth hour, after which a recovery phase appeared. This temporary disturbance of inorganic phosphate excretion was duplicated in two control experiments by the application of fresh pituitary extract to the brain surface. It is concluded that the suggestion that removal of hypophyseal control abolishes the kidney excretion of inorganic phosphate is open to serious question.—L. G. Kilborn.

**The function of the pancreas in tadpoles (*Le fonctionnement du pancréas chez les larves d'Amphibiens*). Functional correlation between the thyroid and internal secretion of pancreas in tadpoles (*Corrélation fonctionnelle le glande thyroïde et le pancréas endocrine chez les larves d'Amphibiens*).** Aron, M., *Compt. rend. Soc. de biol.* 99: 213; 215. 1928.

Glycogen appears in the liver of tadpoles just before metamorphosis. The pancreas is essential for this appearance of sugar but not for metamorphosis. Feeding thyroid just before metamorphosis increases the glycogen in the liver. —J. C. D.

**The effect of hypodermic insulin on the fasting blood sugar in normal and diabetic subjects in relation to percentage normal weight.** Bartlett, W. M., *J. Lab. & Clin. Med.* 12: 115. 1926.

Blood sugar curves following hypodermic administration of insulin are reported in 37 subjects. Underweight normal subjects and underweight diabetic subjects were found most sensitive to the blood sugar lowering effect of insulin. Obese normal subjects are the least sensitive to insulin. The effect of insulin occurs most slowly in obese diabetics and normal subjects of normal weight. The blood sugar curve following insulin is not specific enough in the diabetic patient to be used as a diagnostic test.—I. B.

**A contribution to the nature of diabetes. A mathematical derivation of the blood glucose curve.** Ervin, D. M., *J. Lab. & Clin. Med.* 12: 318. 1927.

By investigating mathematically the condition of diabetes from the blood glucose curve, no evidence of the failure to burn glucose can be obtained. The curve depends upon a decreased rate of glycogen formation.—I. B.

**The stimulation of the external and internal secretion of the pancreas by the same excitant after adrenalectomy (*Excitation des sécrétions externe et interne du pancréas par le même excitant après surrénalectomie*).** Gley, E. and R. Hazard, *Compt. rend. Soc. de biol.* 99: 195. 1928.

In dogs hydrochloric acid intraduodenally produces a secretion of insulin as well as of pancreatic juice. The action of the insulin on the blood sugar is more marked in adrenalectomized animals, because there is lacking the active secretion of adrenin, which normally accompanies and antagonizes a secretion of insulin.—J. C. D.

**Studies on inhibition of insulin activity.** Karelitz, S., P. Cohen and S. D. Leader, *Proc. Soc. Exper. Biol. & Med.* 26: 11. 1928.

When insulin is mixed with human blood plasma, unwashed blood cells, or pus from suppurated processes, its action is somewhat destroyed. Determinations of the activity of the insulin were made upon rabbits. Plasma from a diabetic and cells from a person with myeloid leukemia caused marked inhibi-



tion of insulin activity. In rabbits injected with typhoid or staphylococcus vaccine, about one half showed a decreased insulin effect 3 hours after vaccine treatment. It is suggested that there is something in human blood plasma which is more abundant in blood cells, more in diabetic blood than in normal blood, and still more in leukemic cells and pus which inhibits or destroys the action of insulin. It is probably more abundant in blood of patients with fever, leucocytosis, suppurative processes, or serum sickness, than in normal state. The extent of inhibition is variable for individuals, but quantitatively proportional to the amount of blood used. The inhibitory substance may be a proteolytic enzyme, because the inhibition is greater with blood cells than with plasma, greater with leukemic cells and pus than with normal blood cells, and because it seems to be stronger during fever or infection or after vaccine injection. Even more significant, with regard to the enzyme-like action, is the experiment in which the plasma or pus heated at 57° for 1 to 2 hours no longer inhibited insulin action.—M. O. L.

**Toxicosis of pregnancy treated with insulin [Fünf und vierzig Fälle von Schwangerschaftstoxikosen (Azidosen) mit Insulin behandelt].** Loeser, A., *Zentralbl. f. Gynä.* 52: 1405. 1928.

A report on 36 patients with vomiting of pregnancy, 2 with eclampsismus, 3 eclamptic and 4 with pregnancy dermatoses. The treatment lasted anywhere from 10 days to 6 or more weeks. Sugar was added either by rectal drip or else intravenously. The author advises the use of 5 units of insulin subcutaneously 15-30 minutes after sugar has been given. He considers that a unit of insulin takes care of 3-5 gm. of sugar. The dosage of insulin used was as high as 40 units per day in two doses. As soon as feasible the sugar is given by mouth. The average length of time of this treatment is three weeks. In eclampsismus or eclampsia one can begin with 20-40 units of insulin using 1-2 gm. glucose per unit. In the most severe cases of hyperemesis, with a marked tissue dessication and a decreased water content of the liver, glucose in weak concentration is given intravenously in order to supply liquids.

—H. J. J.

**Insulin hypersensitiveness: immunologic considerations and case reports.** Tuft, L., *Am. J. M. Sc.* 176: 707. 1928.

Since 1924 only two cases of urticarial reaction to insulin have been reported. The two additional cases reported in this paper were studied immunologically. The first patient was sensitive to several commercial preparations and also to Abel's recrystallized insulin. Beef and pork pancreas gave similar reactions. The second patient was sensitive to commercial insulin but not to the purified preparation of Abel. Both of these patients had a generalized urticaria and edema. Antibodies to insulin protein were demonstrated in the patients' serum. The author believes that insulin proteins derived from various species of animals are immunologically similar.—E. L.

**Some observations on the effect of blueberry leaf extract in diabetes mellitus.** Watson, E. M., *Canad. M. A. J.* 19: 166. 1928.

Blueberry leaf extract appears to exert a beneficial effect in certain cases of diabetes. Its action is not consistent. Its utility is most apparent in middle-aged or elderly patients and in mild cases. It is of no avail in the emergencies and complications of the disease. It may become an adjunct to insulin. These results are based on 16 cases.—A. T. C.

**The use of posters as a method of instruction in a diabetic clinic.** Williams, J. R. and M. Vye., *J. Lab. & Clin. Med.* 14: 57. 1928.

This paper deals with personal instruction to diabetic patients. The authors insist that instructing the patient relative to pitfalls of diet and other matters of daily life, is the basis upon which the success of all other elements in treatment depends. On admission to the clinic the patient is given a loose leaf book consisting of mimeographed instructions. He is taught the principles of food chemistry, metabolism, diabetes and insulin action. Informal talks in the class room and demonstrations in the kitchen and laboratory are given. This is supplemented by the use of more than 100 posters, each containing a striking picture to emphasize the lessons. Some posters indicate the foods that are safe and useful; others show foods which are dangerous and forbidden.

Also posters concerning exercise, tobacco, music, marriage, personal hygiene, the care of the feet, and so on, are employed.—I. B.

**Note on the cause of the increased output of insulin following intravenous injection of non-hypotonic solution of secretin** (*Sur les causes de l'hyperinsulinémie consecutive a l'injection intraveineuse de solution de secretine non hypotensive*). Zunz, E. and J. LaBarre, *Compt. rend. Soc. de biol.* **99**: 335. 1928.

Double subcardiac section of the vagus in dogs does not abolish the increased output of insulin.

**The presence of intra-thymic parathyroid islets and parathyroid-thymic masses in infants** (*Ilots parathyroïdiens intra-thymiques et glandule parathyroïdo-thymique chez le nourrisson*). Duperie, R., *Comptes. rend. Soc. de biol.* **99**: 324. 1928.

Four cases, from a premature foetus to a nineteen-month infant in which these anomalies occurred, are described.—J. C. D.

**The influence of parathormone on bone regeneration.** Fine, J. and S. Brown, *New England J. Med.* **198**: 932. 1928.

In carefully controlled experiments on young dogs, parathyroid extract (Collip's) definitely retarded the regeneration of resected ribs. In older animals the results were not so conclusive but no benefit from the extract could be observed.—J. C. D.

**Parathyroid extract-Collip as a diuretic.** Reitzel, R. J. and C. T. Stone, *J. A. M. A.* **91**: 1238. 1928.

The successful use of parathyroid extract-Collip as a diuretic is reported in the case of a woman with odema and ascites, whose reactions to various other drugs were unsatisfactory.—R. G. H.

**Parathyroid extract and glucose tolerance in diabetes mellitus.** Wishnofsky, M. and J. M. Frankel, *J. Lab. & Clin. Med.* **14**: 34. 1928.

The glucose tolerance test may be considered an index of the amount of insulin secreted. If parathyroid extract increases the potency of insulin, this should make itself evident in a reduction in the height and length of the blood sugar curve and in the amount of glycosuria. The authors did not find this to be the case. Their results are completely at variance with those of Cambridge and Howard and others. If we are to assume that parathyroid extract-Collip constitutes the sole active principle of the parathyroids, then we are forced to conclude that the latter are not concerned with carbohydrate metabolism.—I. B.

**Studies on the action of thyroxine on the animal organism and especially on the heat regulation of warm blood animals** (*Studien über die Wirkung des Thyroxins auf den tierischen Organismus und insbesondere auf die Wärme-regulation des Gleichwarmblüters*). Abderhalden, E. and E. Wertheimer, *Arch. f. d. ges. Physiol.* **219**: 588. 1928.

Repeated injections of thyroxine into dogs, rabbits and guinea-pigs lead invariably to rapid loss of weight, and, if continued, to death; rats and mice are much more resistant. Glycogen, especially liver glycogen, is diminished in all animals, even on a rich diet. When di-iodotyrosine, thyroxine, and thyroid are administered in dosage based on iodine content, the first has a very much slighter action. Extremely slight amounts of thyroxine react on the whole organism of tadpoles and the water-form of axolotl, but frogs and the land-form of axolotl are scarcely affected. While di-iodotyrosine shows an enhancing effect on the action of adrenine on heart muscle, thyroxine inhibits this action. Thyroxine, in concentration of 1 in 6000 to 1 in 10000 diminishes the extent of contraction of the heart without affecting its frequency. Rats treated with thyroxine are more susceptible to an increase of external temperature than are normal animals. The latter can maintain their body-temperature within narrower limits. Mice that have been treated with thyroxine do not become pregnant over a considerable interval.—A. T. C.

The pre-operative treatment of Graves' disease by a combination of iodized fatty acid and vitamins A and D. Adamson, G. L. and A. T. Cameron, Canad. M. A. J. 19: 420. 1928.

"Vitiodum," a combination of vitamins A and D and iodo-jecoleic acid, is as effective as Lugol's solution when administered in Graves' disease. Its beneficial action, and the limits of that action, closely resemble those of Lugol's solution. It did not, in the series of cases examined, produce any gastrointestinal disturbance during or following its action. The results suggest that neither the vitamins nor the iodo-fatty acid alone are effective. They suggest also the desirability of investigating as widely as possible the relation between these vitamins and thyroid and iodine metabolism.—A. T. C.

Conditioned reflexes in thyroidectomized animals. I. (Bedingte Reflexe bei thyreoidektomierten Tieren. I). Asimoff, G., Arch. f. d. ges. Physiol. 220: 350. 1928.

Young thyroidectomized dogs show reflexes conditioned from electric stimuli in like time with normal animals, but they do not have the characteristic efficiency of the latter; secondary reflexes were produced more difficultly. There was only slight improvement with lapse of time.—A. T. C.

Investigations on gas metabolism in recovery from exercise in healthy and sick children (Gaswechseluntersuchungen über die Erholung nach Arbeit bei einigen gesunden undranken Kindern). Bruch, H., Jahrb. f. Kinderh. 121: 7. 1928.

Exercise experiments were carried out with the aid of the Krogh spirometer and the sack method of Douglas and Haldane in 5 children. In a healthy 13 year old boy there was an increase in oxygen consumption, especially with an increase in the amount of work. One child with a hypofunction of the thyroid, and a corresponding low metabolic rate, showed a lowered energy requirement. In comparing this with values obtained in a normal child, it was found that the difference in oxygen consumption during the rest period was not great. The metabolic changes in the myxedematous child simulated those present in a normal child at rest. Similar findings were obtained in an obese child.—M. G. B.

The effect of iodine upon experimental hyperthyroidism in man. Carson, D. A. and W. Dock, Am. J. M. Sc. 176: 701. 1928.

Four cases of human hyperthyroidism with all the attendant symptoms were induced by thyroid medication. Upon the administration of Lugol's solution, two of the patients had no lowering of the basal metabolism. There was a very slight drop in the basal metabolic rate in the first patient, and in the second there was no fall.—E. L.

Myocardial disturbances due to abnormal thyroid function and their management. Christian, H. A., Penn. M. J. 32: 70. 1928.

The frequency of myocardial disturbances associated with abnormal thyroid function varies with the type of the latter. The possibility of later or subsequent cardiac lesions is a vital reason for prompt attention to the basic hyperthyroidism, whether associated with adenomatous or hyperplastic thyroid. Hypothyroidism should likewise receive early attention by appropriate thyroid opotherapy. Goiter not associated with disturbance of thyroid function requires no treatment with respect to prophylaxis of heart disease.—I. B.

Thyroid treatment of alopecia areata. Gordon, M. B., Arch. Dermat. & Syph. 17: 817. 1928.

A case of almost complete alopecia in a young girl is reported. The condition had persisted for nine months in spite of local treatment. The administration of thyroid extract was followed by an immediate improvement, which continued until practically all of the hair had returned. The treatment consisted of thyroid extract, 1/10 gr. twice a day for one week, followed by a period of one week in which no extract was given. The dosage was then increased gradually to 1/8 gr., 1/4 gr., 1/2 gr. and 1 gr., at first twice a day, then three times a day, the weekly alteration being adhered to.—Author's Abst.

**Morphological changes in exophthalmic goiter following the use of Lugol's solution.** Hellwig, C. A., Surg. Gynec. Obst. 47: 173. 1928.

In thirty cases of exophthalmic goiter the thyroids were removed after Plummer's treatment and compared with thirty glands removed without previous iodine medication. Most of the observations described by Rienhoff could not be confirmed. After Plummer's treatment no changes in the vascularity and in the amount of fibrous tissue were found. The acini were not round, smooth-walled or of regular size and form. Neither was the epithelium flat and cuboidal, nor were the nuclei small, irregular and pyknotic. In 84% of the glands removed after Plummer's treatment the only definite difference as compared to untreated cases was found in the appearance of the colloid. The acini of these glands had more and higher concentrated content in spite of the fact that the hyperplastic character of the glands was not altered. These findings corroborate Albert Kocher's observation that in Basedow's disease most of the glands removed after iodine medication show distinctly more stained colloid.—Author's Abst.

**Chemical studies on endemic goiter in Formosa.** Hirohata, R., O. Watanabe and S. Watarai, J. Formosan Med. Soc. No. 276. 1928. Abst., Japan M. World, 8: 216.

The author reports epidemiological, clinical and therapeutic studies on goiter occurring endemically in Formosa. In certain districts there occurred some 1.96 to 32.1%. There is one region in which two-thirds of the inhabitants suffered from the disease. In the therapy of the disease, he concludes that iodine seemed to be most efficacious. He also recommends the use of iodine for prophylactic use.

**Juvenile exophthalmic goiter.** McGraw, A. G., Surg. Gynec. Obst. 47: 25. 1928.

Details, including surgical treatment, are given of two subjects, girls of 6 and 7 years, respectively. Sixty-four cases in the literature are analyzed. The identical nature of juvenile Graves' disease with that of the adult is stressed, along with the importance of following up over a long period of years the effects of operation in such cases.—A. T. C.

**Relative lymphocytosis in hyperthyroidism.** Menkin, V., Arch. Int. Med. 42: 419. 1928.

Relative lymphocytosis was observed in 67% of the cases of hyperthyroidism. Relative lymphocytosis is more frequently seen in patients who have exophthalmos superimposed on the usual clinical signs of hyperthyroidism. In patients with exophthalmos, thyroidectomy decreases the relative lymphocytosis and restores a normal differential formula. It is suggested that the relative lymphocytosis in cases of exophthalmic goiter is due to sympathetic stimulation of lymphoid structures, particularly of the spleen, which causes it to contract, as evidenced by experimental work reported in a previous publication. Some patients with hyperthyroidism but without signs of exophthalmos show a relative lymphocytosis apparently not relieved by thyroidectomy. The mechanism of this type of relative lymphocytosis is not clear. It is suggested that it may be caused by a concomitant hyperplasia of lymphoid structures, such as the thymus.—Author's Summary.

# ENDOCRINOLOGY

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## STUDIES OF THE ENDOCRINE GLANDS

### VII. AN ANALYSIS OF FIVE HUNDRED CASES SIMULATING ENDOCRINE DISORDERS

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#### PART I.

In a series of previous communications an objective method for the diagnosis of endocrine disorders has been outlined (1) and a group of clinical studies reported in which it has been applied (2).

In the large number of patients presenting outward evidence of possible endocrine disease (the present group is drawn from a series of over two thousand cases) it is not surprising that a due proportion of them on thorough examination should disclose a non-endocrine etiology. As our studies are concerned with the accurate differential diagnosis of the several endocrine morbidities, such cases form an intrinsic part of any general discussion. From our point of view they are primary in importance, as the basic principle of the diagnostic method is the proven elimination of all possible non-endocrine causes of an observed given result before it may be adduced to support an endocrine diagnosis. The present communication, therefore, deals with the findings from a number of non-endocrine conditions which either present stigmata offering seeming clinical evidence of the recognized endocrine disorders or duplicate the results of individual tests usually associated with some endocrine malfunction. An illustration of the first could be an obesity deriving from gluttony or an amenorrhea of cardiac or renal origin; of the second, the high basal rate associated with leukemia or the persistent glycosuria deriving from syphilis or a lesion of the central nervous system.

Further, speculative endocrinology has, from time to time, deduced from a single symptom a complicity of one or more ductless glands in a condition of known primary non-endocrine etiology. Objective analysis will confirm or deny the warrant of such inclusion and thus define criteria

for treatment which are beneficial in both a positive and a negative sense. The indiscriminate use of powerful glandular extracts has nothing to recommend it as a practice, while the results of an uncritical polypharmacy may be disastrous.

TABLE I  
ETIOLOGICAL CLASSIFICATION

Group	Pathological Condition Detail	Primary	Cases Second- ary	Total	Group Prim Totals
	Normal Controls	18	—	18	18
Infections	Tuberculosis	19	7	26	56
	Atrophic Rhinitis	4	—	4	
	Arthritis	18	6	24	
	Gall Bladder Infections	10	3	13	
	Primary Focal Infections	5	20	25	
Psycho-Neurotic States	Neuroses	21	1	22	60
	Psycho-Neuroses	21	9	33	
	Psychoses	15	1	16	
Disorders of the Central Nervous System	Primary Lesions of the Central Nervous System	47	3	50	82
	Epilepsy	9	1	10	
	Paralysis Agitans and Parkinson Syndrome	11	—	11	
	Mental Arrest	3	5	8	
	Miscellaneous Nerve Diseases	12	1	13	
Disorders of Metabolism	Malnutrition	11	16	30	35
	Obesity	12	5	17	
	Gout	2	—	2	
	Miscellaneous Bone Diseases	7	3	10	
Disorders of the Cardio-Vascular System	Diseases of Heart	7	2	9	61
	Diseases of Kidneys	22	31	53	
	Cardio-Renal Disease	32	9	41	
Diseases of the Blood	Primary Anaemia	8	—	8	17
	Secondary Anaemia	2	2	4	
	Leukaemias (myel and lym)	6	—	6	
	Haemophilia	1	—	1	
Tumors	Tumors, Malignant	6	—	6	20
	Tumors, Benign	6	4	10	
	Goiter, Non-Toxic (1)	8	—	8	
Miscellaneous Diseases	Syphilis (acquired and congenital)	43	14	57	43
	Diseases of the Eye	5	9	14	5
	Diseases of the Ear	57	8	65	57
	Diseases of the Skin	17	6	23	17
	Diseases of Gastro-Intestinal Tract	10	5	15	10
	Diseases of Pelvis	6	4	10	6
	Asthma	11	1	12	11
	Intoxications	2	4	6	2
	Total	500	180	680	500

(1) Thyroid enlargements of endemic type with no evidence of any functional aberration

For these several reasons, the cases presented in the series cover a wide range of disease conditions. Information concerning the general metabolism of some of these is a by-product of the primary investigation and will be discussed at another time. Not infrequently, in addition to the primary morbidity, a secondary condition would be apprehensible, of sufficient importance to warrant its inclusion in the general disease picture. These could be concomitant or resultant, but in either case they produce

symptoms which constitute an integral part of the general condition as presenting for diagnosis. To simplify later discussion, the etiological classification of the five hundred cases may be presented in tabular form.

The group classifications are intended only for convenience and are in some measure arbitrary. Other groupings would be equally open to criticism and would fail to embody the features upon which emphasis is to be placed. The figures presented have but minor statistical value as indicating relative incidence. The group of ear cases, for example, constitute a portion of a study on otosclerosis which has been reported in part elsewhere (3). Other individual conditions represent beginnings of studies which are now under way, as the Parkinsonians, the primary anaemias, and the leukaemias. Where selection has thus been exercised the number of cases recorded is of no significance. All of them, however, fall in on of the several categories outlined above.

Following the practice of the earlier papers in this series, a few of the physical measurements and significant statistics are collated in tabular form. To conserve space, the weight, chest and lung volume comparisons, using Dreyer's and West's standards under limitations already described, are also included.

TABLE II  
PHYSICAL MEASUREMENTS AND "VITAL CAPACITY" COMPARISONS

No	Sex		Obs	Age	Height	Sitting Height	Chest	Weight	Lung Volume
508	M	F	High	75	193	100 5	125	145 0	3600
	97%	33%	Low	1	113	60	53 5	19 2	300
			Average	36 yrs	164 cm	87 cm	79 cm	60 2 cm	2950 cc
Sitting Height In lev			' Vital Capacity '				+56	+109	+23
0 530			High (%)				-23	-40	-89
			Low (%)				+9	+18	+5
			+Average (%)				52	14	15
			%				-7	-12	-24
			-Average (%)				18	56	85
			%				+2	+1	-20
			Net Average						

The female dominance in the sex proportion has already been commented on in the earlier papers where, in the endocrine conditions discussed, it is even more striking. That individual conditions fail to show this disparity (Syphilis: males, 28; females, 29) is lost in the method of presentation. Diseases of the female pelvis obviously play no part in our figures (see Table I). We are inclined to the belief that a more frequent resort to medical aid on the part of the female is a definite although un-evaluable factor.

The ages show a wide range, although in fairness it must be said that young children play but a small part in the series. This is determined in no small measure by the inability of the young to give that measure of co-operation which is essential for the performance of the tests. Further,

the standards for childhood lack the clarity of outline determined for the adolescent and the adult. We have experienced the greatest difficulty in obtaining opportunity to study healthy children in order that such criteria might be established. For this reason we have been obliged, with much regret, to limit our studies, in largest measure, to those groups in which normal performance and the deviations induced by disease have both been defined by actual test and observation.

Extrapolation is always hazardous and peculiarly so when one must bridge so active a period of physiological readjustment as the early years of puberty. In the present series, only eleven children are less than eleven years of age, and of these but two are less than eight. These were two boys, respectively four and six, but both presenting unusual mental maturity coupled with an even more unusual capacity for obedience. In both cases the tests were entirely successful. The popular encouragement to self-expression in early childhood has deprived us vociferously of a number of potential studies.

The several physical measurements show an equally wide range. The maximum weight record of 145 kgm. was that of a so-called normal giant, a man of huge frame and complete normality of physical function. The averages throughout are definitely normal when due allowance is made for the relative sex influence in determining certain ratios. For example, the chest measurement predicted from the sitting height would be 82.8 cm. for the male and 75.5 cm. for the female (Dreyer). Weighting for relative sex influence, the predicted value becomes 78.2 cm., while the observed rounded average is 79 cm. This serves to illustrate both the absorption of large individual variations in any average computation and equally, the significance attaching to the variations (when presented by a single group), even though they be of small magnitude. This latter point has been stressed in the earlier endocrine papers. In them also has been emphasized the greater significance of relative values when comparisons are with standards making allowance for certain of the fixed variables. The so-called "Vital Capacity" comparisons embody this principle and the data gather an added import. The cases in the series show a rough equality in over- and under-weight. The former is the smaller group but is free from the natural limitation implicit in those below prediction; as a result, it balances in amount what is lacking in number and the net average deviates but 1 per cent away from prediction. The chest measurements, as is to be expected, parallel those for weight. With the lung volume, however, there is a sharp and significant departure from the normal. Only 15 per cent exceed prediction and then only to an inconsiderable amount. The net average shows a drop of 20 per cent from predicted to observed values. As has been previously stated, we have found Dreyer's male "A" and female "B" standards most nearly to conform to normal American relationships. In a recent monograph Myers (4) has presented a most valuable summary of the influence of cardiac and pulmonary disease on this quan-



tity. He concludes that lung volumes falling 15 per cent or more below the predicted level require careful examination. In addition to a variety of significant pathological states influencing lung volume unfavorably, he records others, chiefly residua, which are devoid of clinical import. Malingering and lack of co-operation are cited as factors to be reckoned with.

In our own experience the second of these assumes a very marked significance and one of us has emphasized its influence as clearly indicated where a long series of observations are made on the same patient (5). The asthenia of severe illness, irrespective of character, is a powerfully inhibiting influence (eight cases of primary anaemia averaged —41 per cent, and six of leukaemia—38 per cent), and low values are to be interpreted as due in part to weakness. In the present compilation, the importance resides in the low average produced by such a variety of conditions of which cardiac and respiratory conditions are only a small part.

As the cases of this group were studied primarily for their simulation of endocrine conditions or the possible presence of an endocrine element in the etiology, a brief comparison may be made with the results of the several endocrine series.

TABLE IIa  
"VITAL CAPACITY" COMPARISONS

	Gland				
	Function	Pituitary	Thyroid	Ovary	Adrenals
Weight.....	—	+22	+10	+ 5	—11
	±	+12	+ 6	—	—
	+	+ 7	— 3	—	—
	Weighted Average..	+14	+ 7	+ 5	—11
Lung Volume....	—	—19	—22	—19	—18
	±	—19	—22		
	+	—16	—39		
	Weighted Average...	—18	—24	—19	—18

The obesity of the pituitary and the emaciation of the adrenal cases show marked divergence from the non-endocrine average. The tendency of the hypofunctional endocrine states (exclusive of the adrenal) is here evidenced.

With the lung volume measurements, on the other hand, only the thyroid exceeds the loss shown by the non-endocrine group. It is striking that the subjects of adrenal deficiency in whom asthenia is a uniform and highly significant observation, show slightly smaller loss than does the group under discussion. The lack of representative character determined by the meager number of adrenal cases may conceivably be balanced against the appreciable number of approximately normal individuals which tend to raise the average in the non-endocrine group.

The results of analyses and tests using the urine as the medium of response, are collected in Table III.

TABLE III  
URINE MEASUREMENTS

Urine Analysis		Phenol Sulphone Phthalein		Nitrogen Partition	
Observation	Amt.	Observation	Amt.	Observation	Amt.
Volume.....High (cc.)...	1600	1st Hour....Av. (%)....	35	Total N <sub>2</sub> ....Av. (gms.)...	9.00
Low (cc.)...	300	2nd Hour....Av. (%)....	20	Urea N <sub>2</sub> ....Av. (%)....	81.1
Average(cc.)	1210	Total.....Av. (%)....	55	Uric Acid....Av. (%)....	2.3
		High.....	90	Ammonia....Av. (%)....	3.8
Spec. Grav...High.....	1.037	Low.....	8	Creatinin....Av. (%)....	4.5
Low.....	1.005			Residual....Av. (%)....	8.3
Average.....	1.018			% = or > 9% (.....)	48
		Urea Curve			
Albumin (%).....	26	Normal (%).....	54	Misc. Tests	
Casts (%).....	19	Delayed (%).....	11	Amylase Index, Av.....	11
Sugar (%).....	9	Progressive (%).....	9	Salol, Av. (min.).....	71
"Urobilinogen" (No.)....	4(1)	Low (%).....	26		

(1) Four Cases of Primary Anaemia.

While certain of the cases showed a marked polyuria, the average elimination conforms to normal figures, as does that for the specific gravity. The appreciable percentage of cases showing albuminuria and casts includes not only the established kidney cases but numerous others in which nutritive disturbances, faulty posture, and similar factors are operative. The cases exhibiting glycosuria are interesting and significant. It is understood, of course, that no cases of pancreatic diabetes are included. They were excluded from the endocrine studies for reasons that have already been discussed and naturally may form no part of a group of non-endocrine diseases. The allocation of the glycosurias to the major etiological headings is informative.

TABLE III-a

Condition	No. of Cases
Lesions Central Nervous System.....	13
Psychoses .....	4
Syphilis .....	8
Gall Bladder Disease.....	4
Normal Pregnancy.....	1*
Asthma (Adrenalin).....	1
Primary Anaemia.....	2
Leukaemia .....	2
Malignant Neoplasm.....	2
Total.....	37

The remaining eight cases were scattering and no direct cause of the glycosuria was ascertained. Malnutrition was not impossibly the cause in the majority of them. Alcoholism may have been a factor in two cases. While certain of these conditions are generally recognized as causative of low-grade glycosuria (lesions of the brain, gall bladder, pregnancy, etc.), comment may be permitted on certain others. In our experience, a slight

\*Glucose and not Lactose.

glycosuria is the frequent accompaniment of syphilitic infection even when no evidence can be obtained of active involvement of the nervous system. It is also noteworthy that one-third of the leukaemic cases, one-fourth of the primary anaemias, and one-third of the cancer cases presented the same condition.\*

As the endocrine cases (exclusive of the thyroid) show an incidence of nearly 25 per cent, the significance of the present observation is patent.

Reverting to Table III, another interesting observation lies in the occurrence of a positive "urobilinogen" test in four cases of primary anaemia. This test was first offered as an indication of liver disease but was shown by us to occur frequently in pituitary disorders. That positive response is not conditioned solely by the presence of urobilinogen in the urine, is highly probable. Like many color tests, the reaction is probably not specific.

The Phthalein test offers nothing distinctive, the low normal value agreeing with the findings in the endocrine series. The provocative urea curves equate well with the urine findings, one-fourth of them showing poor elimination. Low values do not always imply a lessened kidney permeability, as a number of cases of partial protein inanition exhibit the same phenomenon. Whether an analogy to the condition postulated in Folin's theory (6) of tissue absorption of ingested carbohydrate is operative here, remains to be determined. The relatively normal salol value is a modest bit of evidence for relative kidney integrity as it measures this function primarily, the indication of the level of gastric motility depending on normal elimination.

The Nitrogen Partition and its implications have been discussed in detail in the earlier papers. In brief, a residual nitrogen fraction in excess of 9 per cent is to be regarded as an evidence of disturbed metabolism. While high values are found in all endocrine conditions and their incidence is frequent,† we regard the phenomenon as an indication of the influence of ductless glands on general metabolism rather than a pathognomic sign of endocrine malfunction. The data given above offer strong supporting evidence for this contention. While the average level is below the limit set for normality, in practically half of the cases it has been exceeded. The allocation of these cases to the several etiological groups is interesting.

\*Since the subject is shortly to be considered elsewhere no further discussion is necessary at this time.

†The endocrine relationships are as follows:

TABLE III-b

<i>Gland</i>	<i>Pituitary</i>	<i>Thyroid</i>	<i>Ovary</i>	<i>Adrenal</i>
Residual N <sub>2</sub> , Av.	9.4%	10.3%	9.1%	9.3%
%=or> 9%	51	61	48	56

Only in subjects of thyroid and adrenal involvement does the incidence exceed significantly that of the non-endocrine subjects, although all of the glands exhibit averages above the normal limit.

TABLE III-c

Etiology of Non-Endocrine Cases Exhibiting High Urinary Residual Nitrogen.

Etiological Group	Total Cases	No. with High N <sub>2</sub>	Per Cent
Primary Infections.....	53	27	51
(a) Secondary to other disease...		9	
Psycho-Neurotic States.....	60	36	60
Lesions of Cent. Nerv. System.....	44	26	59
Epilepsy .....	9	7	78
Park. Syn. and Paral. Agit.....	10	4	40
Syphilis .....	42	24	57
Diseases of Kidney.....	50	29	58
(a) Secondary to other disease...		24	
Anaemia (prim. and sec.).....	10	7	70
Leukaemia (myel. and lym.).....	6	6	100
Tumors (mal. and benign).....	12	8	67
Goiter, non-toxic <sup>1</sup> .....	8	4	50
Normal .....	18	0	0

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NOTE—Total of 235 cases in 489 recorded.<sup>2</sup><sup>1</sup>Concerning the propriety of the inclusion of this group, see text.<sup>2</sup>The remaining 24 cases were too widely scattered to possess any etiological significance.

The high incidence in epilepsy, leukaemia and the tumor group is striking though it exceeds, in degree only, several of the other groups which show a frequency of over one in every two cases. As an evidence of metabolic disturbance we feel the case established; as a differential diagnostic point it is wholly non-specific. Undoubtedly had this investigation extended to other morbid states, additional conditions would be included. It is perhaps important that the so-called diseases of metabolism

TABLE IV  
BLOOD CHEMISTRY (AND SEROLOGY)

	High	Low	Average	Deviation	Per Cent
Non-Protein Nitrogen... (mgm)	128	11	32	> 35 mgm	20
Urea Nitrogen.... (mgm)	75	6	15	> 17 mgm.	20
Uric Acid.... (mgm)	7 1	1 7	3 5	> 1 mgm	10
Creatinin. .... (mgm)	5 0	1 0	1 5	—	—
Residual Nitrogen ... (mgm)	>50	< 5	15 2	—	—
Sugar. .... (mgm)	133	68	97	>120 mgm	1
				< 80 mgm	3
			6		
			10		
			8		
			1		

(1) All cases demonstrating Nephritis and Gout have been deleted.

are not represented in the group. The term “metabolism” is a comprehensive one and includes a myriad of interrelationships. A possible dominance of the nervous system might be deduced from these figures but the seeming relationship may be only an arithmetical artefact. Many thousands of diverse observations would be necessary to resolve the question with any measure of certainty.

As the precursor of the urine, the blood in its chemical aspects may next be considered.

Since renal disease plays a not inconspicuous part in this series, it is to be expected that high values will appear in the individual observations. Inspection of the superior limits shows values compatible with severe but not terminal nephritis. Twenty per cent show values for non-protein and urea nitrogen in excess of the conventional normal

Significant from the differential standpoint is the relatively low incidence of high uric acid values. A high blood uric acid with relatively normal non-protein nitrogen has been observed in pituitary malfunctions, and in the proven absence of nephritis and gout may possess definite diagnostic value. The relative infrequency in the non-endocrine group enforces the observation.

Another significant feature is the small percentage of blood sugars falling outside the conventional normal limits. Further, the maximum individual deviations observed are of the order of  $\pm 10$  to 15 per cent, and those were recorded in single cases only. If the average values be taken for the several quantities, the entire picture is one of the most rigorous normality. Six per cent of the cases showed positive Wassermanns, confirmed in the ten most recent cases by a similar response to the Kahn presumptive test. Incidentally, the correlations in the series are complete.

In addition, eight other cases gave positive results, indicating neurosyphilis, in the examination of the spinal fluids. For obvious reasons, lumbar punctures were not a part of the invariable routine, but were performed wherever history, physical examination, or laboratory picture gave evidence of a possible specific condition. A few Schwartz-McNeil tests were made, giving a positive response in only one case. Of the forty-two cases in which syphilis was the primary condition, thirty-eight were confirmed by the positive serological findings, while in the remaining four the diagnosis was equally certain although treatment had obliterated the serum response

The character and amounts of the several form elements of the blood is always important, and in not a few conditions determine the final diagnosis. Our own observations are assembled in Table V.

TABLE V  
BLOOD MORPHOLOGY

General Examination		Amount	Differential Count <sup>(1)</sup>		Per Cent	
Haemoglobin	High (%)	>100	P M N	Neutrophiles	Average	61
	Low (%)	15	% >75%		.	6
	Average (%)	87				
Erythrocytes	Average (10 <sup>6</sup> )	4.85	Lymphocytes	.	Average	31
			% >33%		.	43
Color Index		0.90	Eosinophiles	.	Average ..	2
			Net <sup>(2)</sup> % = or >3%		.	15
Leucocytes	Average <sup>(1)</sup> (10 <sup>5</sup> )	8.1	Endothelials	..	Average	6

<sup>(1)</sup> Omitting data of 6 cases of I leukaemia

<sup>(2)</sup> Cases in which a non-endocrine cause of eosinophilia was demonstrated, have been deleted.

In compiling these averages, the few cases of primary anaemia have been included but, as is stated in the footnote, the cases of leukaemia were deleted from the leucocyte average. Typical observations in this group were 92,300 and 82,900 in two representative cases. The inclusion of these would change the average by nearly 10 per cent and render it by so much the less representative of the entire group. Taking the picture presented by the average values, the general impression is one of normality. The haemoglobin value is somewhat low, but the cases composing the group included many in which slight secondary anaemia is a common feature. This is also reflected in the red count.

The differential count, from its relative character, is perhaps somewhat more significant. The lymphocyte average is normal in contradistinction to that in the endocrine cases as shown in Table V-a.

TABLE V-a  
Lymphocyte Count Averages.

Gland	Pituitary	Thyroid	Ovary	Adrenal
Lymphocyte %.....	36	37	35	27
%=or > 33% .....	59	60	56	50

While these values exceed those of the non-endocrine group, the differences are not great. Further, while the latter series averages less than the arbitrary "normal," nearly half of the cases in the group exceed this limit. An allocation of these cases to the several general diagnostic groups is presented in Table V-b.

TABLE V-b  
Etiology of Non-Endocrine Cases with Lymphocytosis.

Etiological Group	Total Cases	Cases with Lymphocyt.	Per Cent
Primary Infections.....	53	26	49
(a) Infection (secondary) .....	..	10	..
Psychoneurotic States.....	60	36	60
Lesions of Cent. Nerv. System.....	44	19	43
(a) same, secondary.....	..	1	..
Epilepsy .....	9	2	22
Park. Syn. and Paral. Agit.....	10	9	90
Syphilis .....	42	19	45
Diseases of Kidney.....	50	24	48
(a) same, secondary.....	..	26	..
Anaemia (primary).....	8	5	63
(secondary) .....	2	0	0
Leukaemia (myel. and lymph.).....	6	3	50
Tumors (mal. and benign).....	12	3	25
Goiter (non-toxic).....	8	3	38
Normal .....	18	0	0

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NOTE—Total of 215 cases in 489 recorded. The remaining 29 cases were widely scattered.

The same general diagnostic groups are the representatives in this compilation as in that dealing with the high residual nitrogen. Further, in certain members the correlations are definite, as in the groups of infections, the mental and nervous disease group, and less strikingly in the syphilitic, cardio-renal groups, and those cases with lesions of the central nervous system. Equally, if not more significant are the divergences from parity. For example, the epileptic group shows a lymphocytosis far less frequently than a high residual nitrogen (78 per cent against 22 per cent), while the Parkinsonians (with Paralysis Agitans) exhibit more than double the incidence. Five in eight of the primary and neither of the two established secondary anaemia cases show it. There is a markedly lower occurrence of a lymphocytosis in the tumor group.

Whatever the exciting cause, it is obvious that two widely different mechanisms must be involved in the production of the two phenomena. As the matter contains certain possibilities, a still more detailed analysis may be permitted. Certain diagnostic groups have been shown to exhibit a practically equal incidence of the two aberrations, while in others there is a well defined difference. The relative frequency in which both are shown by the same individual has been determined.

TABLE V-c  
Correlation of (a) High Residual Nitrogen  
with  
(b) Lymphocytosis in Non-Endocrine Group.<sup>1</sup>

Etiological Group	1 Total Cases	2 With a, b, or Both	3 With a + b	4 Per Cent + Cases	5 Per Cent All Cases
Infections .....	89	58	14	24	16
Psycho-Neurotic States.....	84	53	19	36	23
Lesions of Cent. Nerv. System...	47	35	11	31	23
Epilepsy .....	10	7	2	29	20
Park. Syn. and Paral. Agit.....	10	10	3	30	30
Syphilis .....	56	31	12	39	21
Diseases of Kidney.....	90	82	21	27	23
Anaemia .....	12	8	3	38	25
Leukaemia .....	6	6	3	50	50
Tumors .....	12	8	3	38	25
Goiter, non-toxic.....	8	6	1	17	13
Miscellaneous .....	..	..	10	..	..
			<hr/> 102		

<sup>1</sup>Both Primary and Secondary conditions are included.

In the various correlations, leukaemia leads easily, which is probably attributable to the fact that all cases show a high residual nitrogen. Obviously the correlation depends also on the proportion of the lymphatic type. Comparing frequency with incidence of one or the other condition (column 2 with 4), syphilis with low and anaemia and tumors with moderate frequency show a high correlation. On the other hand, the Parkinsonian (and Paralysis Agitans), kidney and goiter cases, show high incidence and

moderate or low correlation. Lesions of the central nervous system show a moderate frequency and a like correlation. The nervous and mental diseases with low, and epilepsy with moderate frequency show respectively moderate and low correlation. The infection group is consistently low throughout.

The authors offer no theory to explain these phenomena at this time but confine themselves to presenting the facts. One more comparison is suggestive, namely, the relative incidence in the several endocrine groups in comparison with the present diverse assembly.

Gland	N <sub>2</sub> Increased Lymph, Normal	N <sub>2</sub> Normal, Lymph, Increased	Both Increased
Pituitary .....	19%	27%	33%
Thyroid .....	23%	22%	39%
Ovary .....	21%	28%	28%
Adrenal .....	31%	25%	25%
Total Endocrine <sup>1</sup> .....	20%	27%	33%
Non-Endocrine .....	27%	23%	21%

<sup>1</sup>Weighted for relative representation.

The greater measure of correlation in the endocrine group is apparent. Reverting for a moment to Table V, it will be seen that not only is the average eosinophile value a normal one, but the percentage exhibiting eosinophilia is much less than with the endocrine group, particularly in the adrenal and pituitary cases.

A very definite influence on the respiratory metabolism is exercised by the members of the endocrine group. While the striking changes produced by aberrant thyroid function has tended to minimize the attention devoted to the other members of the concert, they all participate and determine certain highly characteristic deviations from the predicted normal. Improvement in accuracy and simplicity of determination of the magnitude has extended the study into numerous other fields, and it is recognized today that a variety of non-endocrine causes may produce deviations in the basal rate which equate in magnitude with those of endocrine origin. In any method of differential diagnosis employing basal metabolism tests, the non-endocrine become equally important with the endocrine cases and must be reckoned with primarily in any interpretation of data. Many of the early data relative to the basal rate in disease derives from duBois and his associates (7) at the Russell Sage Institute of Pathology, although Magnus Levy (8), beginning in 1894, established trends of deviation in a large number of disease conditions. Later workers have added much, and there is today a steadily growing and extensive literature which has been well reviewed in several recent monographs.\*

The influences that have been observed can best be discussed after consideration of our own data. Because they are pertinent to the basal rate determinations, certain concomitant observations are likewise recorded.

\*See among others Graefe (9), Boothby and Sandiford (10), McCann (11) and Selected Chapters in "Endocrinology and Metabolism" (12). See also the numerous publications of W. O. Atwater, F. G. Benedict, and their associates for many fundamental studies.



The observed rates vary from +49 per cent, which would equate with a moderate hyperthyroid condition, to -25 per cent, a level which might be associated with failure of any of the four principal endocrine glands (pituitary, thyroid, ovary, adrenal).\*

On the other hand, the average of nearly half of the cases showing rates above prediction is only +7 per cent, while the somewhat larger group falling below the base line gives the same minus average. The net average deviates but 1 per cent from prediction. Further, 80 per cent of the cases fall within the conventional normal zone. With the exception of a few conditions which have been previously demonstrated to influence respiratory metabolism, the great majority of the cases fail to produce deviations which could confuse an endocrine diagnosis.

To specify the disturbing influences and indicate their extent, an analysis of our own data may be made and discussed with running comment on previously recorded observations. It should perhaps be empha-

TABLE VI  
RESPIRATORY METABOLISM

Observation	Amount	Observation	Amount
Basal Metabolism		Blood Pressure	
Deviation.....High (%).....	+49 <sup>(1)</sup>	Systolic.....Average (mm.)..	124
Low (%).....	-25	% = or > 150 mm.....	11
+Average (%).....	+ 7	% = or < 110 mm.....	24
%.....	44	Diastolic.....Average (mm.)..	73
-Average (%).....	- 7	% = or > 100 mm.....	6
%.....	56	% = or < 65 mm.....	27
Net Average.....	- 1	Pulse Rate.....Av. (per min.)..	77
% above +10%.....	6	% = or > 80.....	38
% between +10% and -9%.....	80	% = or < 70.....	30
% = or below -10%.....	14	Respiration Rate..... Av. (per min.)..	15
Alveolar CO <sub>2</sub> .....Average (mm.)..	39	% = or > 20.....	13
% > 35 mm.....	45	% = or < 10.....	9
% = or < 30 mm.....	7	Temperature.....(deg. F.).....	98 2

(1) Lymphatic Leukaemia.

sized that the component cases of the groups here presented have been demonstrated to be free from endocrine complication. Where such exists, the case has been listed under the endocrine focus participating. To illustrate, a certain small percentage of arthritic cases have well established thyroid failure and improve on thyroid medication. Similarly, we have demonstrated that gall bladder (and liver) disease may accompany thyroid failure and seemingly be closely associated with it in a causal or resultant relationship. The coincidence of the two conditions has been remarked by others. The simultaneous presence of an endocrine malfunction, coincidentally with a well-defined non-endocrine disease, may well account for some of the contradictory observations recorded in the literature.

Tuberculosis in its early stages at least and without a marked febrile condition, seemingly tends toward a normal or slightly depressed basal rate. This is in accord with the earlier reports. The high rates are usually

\*For reasons earlier discussed, the pancreas has played no part in this study.

TABLE VI-a  
ETIOLOGICAL ALLOCATION OF BASAL RATES

Group	Pathological Condition	Detail	High	Low	Basal Rates		Total	Group Average
					+	-		
Infections.....		Tuberculosis <sup>(1)</sup> .....	+12	-19	6 = + 5	11 = - 9	17 = - 4	- 3
		Atrophic Rhinitis.....	+11	- 3	3 = + 9	7 = - 3	4 = + 6	
		Arthritis.....	+ 8	- 8	6 = + 3	12 = - 5	18 = - 2	
		Gall Bladder Inf.....	+ 6	-12	2 = + 4	6 = - 8	8 = - 5	
		Focal Infection.....	+ 6	-12	3 = + 2	2 = - 9	5 = - 2	
Psycho-Neurotic States.....		Neuroses.....	+12	- 8	10 = + 7	11 = - 5	21 = + 1	- 1
		Psycho-Neuroses <sup>(2)</sup> .....	+10	-10	11 = + 5	12 = - 5	23 = - 1	
		Psychoses.....	+17	-21 <sup>(3)</sup>	7 = + 8	8 = - 8	15 = - 1	
Central Nervous System.....		Lesions of Central Nervous System.....	+19	-20 <sup>(4)</sup>	19 = + 9	25 = - 7	44 = + 0	± 0
		Epilepsy.....	+14	- 9	4 = + 8	5 = - 5	9 = + 1	
		Parkinsonian Syndrome and Paralysis Agitans.....	+105 <sup>(5)</sup>	- 3	8 = +30 <sup>(4)</sup>	2 = - 3	-	
Kidneys.....		Diseases of Kidneys.....	+15	-17	13 = + 7	9 = - 7	22 = + 1	± 0
		Cardio-Renal Disease.....	+20	-20	14 = + 7	14 = - 8	28 = - 1	
		Syphilis.....	+17	-23	20 = + 6	22 = -11	42 = - 3	
Blood.....		Anaemia (primary).....	+ 7	-25	5 = + 4	3 = -14	8 = - 3	- 3
		Leukaemia.....	+49	- 4 <sup>(6)</sup>	5 = +31	1 = - 4	6 = +25	
		Tumors.....	+14	-15	6 = + 7	5 = - 8	11 = ± 0 <sup>(7)</sup>	
		Non-Toxic Goiter.....	+10	-11	3 = + 4	5 = - 6	8 = - 2	- 1
		Obesity.....	+ 8	-11	6 = + 3	6 = - 4	12 = - 1	
		Asthma.....	+ 9	-10	3 = + 4	8 = - 6	11 = - 3	

(1) Afebrile. Average Temperature = 98.4  
 (2) One case omitted (+20) where patient restless and value obviously too high.  
 (3) Marked malnutrition. Next low case -9.  
 (4) Brain Tumor.  
 (5) See text (6 cases = +11).  
 (6) During remission period. High rates observed later.  
 (7) Basal Rate not obtainable in one case.

but the expression of the influence of fever, as duBois has so clearly shown. Graefe's few severe cases would seem to offer an unexplained exception.

Uncomplicated arthritis apparently arising from infective processes is rigidly normal in this series. The low values which are occasionally recorded are possibly due to an endocrine element. The same is true for cholecystitis, although malnutrition may operate in this condition to lower the basal rate. The group which we have conventionally designated as "Infections" shows no evidence of significant departure from prediction.

In the next group of nervous and mental states two complications may arise. First, some cases presenting one or another of these conditions may have a definite endocrine complication which seemingly is causal (see paper on Thyroid in this series, *i.e.*). That the speculative practice of ascribing all mental disease to endocrine aberration is unwarranted, the cases listed above will prove. Again at the risk of over emphasis it may be said that the final diagnosis rests on a very complete clinical and laboratory study in which each observation is interpreted in the light of numerous others. The endocrine complicity is neither included nor excluded on the basis of a single test, and certainly not on that of a single opinion. If this current study of approximately two thousand cases (supported by nearly two thousand more since this compilation was begun) can be taken as warranting a tentative opinion, the percentage of psychotic cases which can be proven to derive from endocrine malfunction is not large. Equally, however, a definite number do demonstrate an endocrine etiology and this factor must be considered. The second complication is implicit in the nature of the case. Slight movement will exercise a wholly detrimental effect on the accuracy of the test, and nervous instability may determine muscular efforts too slight to produce gross movement but ample to vitiate the measurement. We have deleted two of our cases for this reason, and regard many of the retained values as probably somewhat above the truth. Due attention to this disturbing element and the education of the patient by repeated tests as a means of correcting it, will give fairly representative values. We feel, in the cases reported, that gross error has been eliminated.

So comprehensive a term as "lesions of the central nervous system" naturally embraces a wide variety of conditions. In some of the brain tumor cases the lowered rates were possibly attributable to pressure influencing the pituitary unfavorably. In one case which we were privileged to study and which gave all of the typical evidences of pituitary disease, autopsy demonstrated that the neoplasm localized outside of the gland but had produced a sufficient intracranial pressure seemingly to determine a typical pituitary dysfunction. The cases here listed gave no evidence of pituitary participation other than the possible influence on the basal rate. The group of epileptics is also normal, although in several cases degenerative changes had resulted from a long standing condition.

The group of Parkinsonians (including a few cases of paralysis agitans) are extremely interesting. Very high values were obtained in a few cases but we were fortunate enough to secure several in which the

syndrome was in its incipency.\* These cases showed values which were normal or, at the worst, but slightly above the normal level. This seems to confirm the opinion of Magnus Levy (13), although by no means controverting the later opinion of Graefe (14). In this connection, a case of paralysis agitans, observed in the course of another study, offers information of value. The patient, a man in the late fifties and with a very pronounced tremor, was studied at two-week intervals for a considerable period. His prevailing rate lay with surprising uniformity between +60 per cent and +70 per cent. At the time of one test in the middle of the series, it was noted that his tremor was perceptibly less, and on this day the rate dropped to +24 per cent. When next seen the tremor had resumed its wonted course and the rate was +64 per cent. A single observation of this character is interesting even though it cannot be regarded as decisive.

Our renal cases show the general normality that has been recorded by others. Edema was not a complication in this group. The cardio-renal group practically repeats the kidney observations, although the extreme limits are slightly wider. Individual cases, however, may well have some slight superimposed effect (low protein diet, for example, in a considerable number of these cases) which will in summation exceed the normal limits. We feel that this explains our own cases showing a hypofunctional level. The actual numerical values of the low readings are more significant than the high, for reasons that have already been discussed.

The syphilitic cases show a definite downward tendency. Twenty-two cases average -11 per cent, and in this group are several with rates of about -20 per cent. When taken in conjunction with the influence on carbohydrate metabolism frequently exercised by this disease, it is evident that syphilis may simulate endocrine disease in some measure. While the serological tests should preclude frequent grave error, the necessity for their performance is patent.

Primary anaemia has severally been recorded as ranging from about -20 per cent to +30 per cent, both extremes suggesting a possible endocrine involvement. In our own very small group but one case falls outside relative normality, and as this is to be discussed later, comment may be postponed.

The tumors, both malignant and benign, fall reasonably within the normal zone. Boothby and Sandiford report one case of Hodgkin's disease with a rate above +20 per cent. Our two cases gave readings of, respectively, +3 and -15 per cent.

The basal rates of the non-toxic goiter cases offer one definite warrant for their inclusion in the non-endocrine group. Physiological obesity, as was earlier shown by Means (15) exercises no detectable influence on the basal rate.† The asthma cases are recorded as the condition is, from time to time, referred to an endocrine origin. The present group gives no evidence of any hormonal influence.

\*The authors wish to express their thanks to Dr. N. H. Garrick for his interest and courtesy in securing these cases for us.

†The cases here listed averaged 101.2 kgm. and 59 per cent above predicted weight.

Reverting to Table VI, it will be noted that while the averages for the Blood Pressure are entirely normal, an appreciable percentage (about one-fourth) show hypotensive levels which might suggest endocrine disease. The Pulse Rates show nearly 70 per cent outside of the range of from 70 to 80. The other findings are essentially normal.

Alveolar carbon dioxide exhibits a normal average, nearly half the cases above the conventional lower limit of normality and but 7 per cent showing a tension suggestive of acidosis. With the number of kidney cases in which a retention acidosis is possible, the value observed is reasonable. While the general picture is a normal one, enough has been shown to indicate that individual cases may far exceed normal limits, and by a fortuitous combination suggest an endocrine malfunction, the non-existence of which can be demonstrated only by a comprehensive study.

The sugar (galactose) tolerance is the sole remaining laboratory test permitting presentation in tabular form.

TABLE VII  
GALACTOSE TOLERANCE

Observation		Unit	Male	Female		
Tolerance Dose....	High. .	gms.	40	40	Summary	
	Low ..	gms.	5	5		
% above Normal. .		%	3	0		
Average Deviation .		%	+33	—		
% equal Normal		%	37	43		
% below Normal		%	60	57	Av Deviation <sup>(1)</sup> > N .	+33
Average Deviation		%	-47	-43	Av Deviation <sup>(1)</sup> < N .	-45

(<sup>1</sup>) Not weighted for numbers

The test is one of great differential significance, as there is not only an intrinsic sex difference, but each of the important endocrine glands exercises a definite and characteristic influence on the amount of the sugar capable of utilization. In the table given above, slightly less than 40 per cent of the cases are considered. The data here reported are derived from the routine work of a consulting diagnostic service. The sugar test, which requires two or three days for performance, is performed only when its indications are essential for the establishment of a diagnosis.

Of the cases examined, less than half showed a normal tolerance. Only two cases showed a tolerance above normal, and those were both advanced cases of chronic interstitial nephritis. Lessened permeability of the kidney rather than heightened carbohydrate tolerance is patently the cause of this observation.

\*As has been stated in the previous papers, the male tolerance is unvarying and at 30 grams. The female, on the other hand, is normal with 20 grams in the prepubertal period, passes during puberty by degrees to 40, the normal adult level, and at the menopause may maintain the adult 40 or more usually, or recede to 30 grams. Pregnancy lowers the tolerance first to 30 and later to 20 with restoration to the normal adult level with the resumption of sexual rest. For this reason, tolerances are expressed in percentage deviation from the individual norm.

The allocation of the remaining one hundred and twelve cases showing a lowered tolerance bears directly on the thesis.

Of parallel observations but a few need be mentioned. Bauer (16) first suggested the use of galactose as the basis of a tolerance test, applying it to liver conditions. His primary contribution was followed by numerous studies, which have been summarized by Wörner (17). Later studies have supplemented and confirmed the earlier opinions. Offenbacher (18) has demonstrated that galactose and levulose are both influenced by liver integrity, while glucose, on the other hand, seemingly is not. Bauer, in a later paper (19), records observations in cases of syphilis and of malignant neoplasm, using a uniform test meal of 40 grams. As an elimination of less than 3 grams was regarded by him as a negative response, his conclusion of normality in these conditions is erroneous. The writer's own

TABLE VIII

Etiological Allocation of Cases with Abnormal Tolerance.  
112 Cases with Lowered Tolerance

Group	
Central Nervous System <sup>1</sup> .....	43 <sup>2</sup>
Psycho-Neurotic States <sup>1</sup> .....	15
Syphilis .....	15
Primary Anaemia.....	7
Leukaemia .....	4
Tumors (malignant <sup>1</sup> ) .....	3
Asthma (Adrenalin med.).....	2
Gall Bladder (Liver).....	7
Hypertension .....	4
Total.....	100

NOTE—Of the 12 remaining cases, all show a depression of only 10 grams. Two cases with increased Tolerance (males at 40) had advanced Chronic Interstitial Nephritis.

observations show that a significant percentage of syphilitics show a definitely lowered tolerance, and similar findings in malignant neoplasms are confirmed, among others, by Friedenwald and Gross (20) and Langston (21). The observations of Lorenz (22) would seem to indicate a lowered tolerance in certain psychotic states, although Barrett and Serre (23), in dementia praecox, were unable to demonstrate any consistent abnormality in sugar tolerance. Hirose (24), Strauss (25), Wagner (26), and others, have noted depressed tolerance for galactose in the neuroses. O'Hare (27) found abnormal tolerance in one-half of a series of hypertensive cases. Davidson and Allen (28) have shown a lowered tolerance in head injuries, and Kasanin and Garfield (29) observed decreased tolerance, associated with encephalitis, in adults, although the opposite obtained with children.<sup>3</sup> Richard Bauer (30), using 40 grams of galactose as a test meal and regarding an elimination of less than 2 grams as negative, could find no influ-

\*In many of the papers cited above, tolerance was determined by the shape of the sugar curve. Comment has already been made upon the lack of quantitative significance of the single sugar curve. It may be regarded, however, as offering some qualitative evidence of the relationship of the exciting dose to the individual tolerance.

<sup>1</sup>See Table I for composing members.

<sup>2</sup>Percentages are not given as all of the cases in a group did not receive the sugar test

ence on the tolerance in primary anaemia. With the wide range of conditions listed in which a lowered tolerance is a possible or even a probable observation, it is obvious that the test, while of great differential value, requires a variety of supplementary tests for its proper interpretation.

It will be remembered from Table III, that 9 per cent (45 cases) showed glycosuria. While the metabolism of glucose and of galactose, in some measure at least, bespeak different mechanisms, the lowered tolerance for galactose offers a possible explanation of the glycosurias observed. The whole question of non-diabetic glycosuria\* is implied in the observations of this and the several endocrine series. Seemingly many agencies operate to lessen the power of the body to utilize carbohydrate. While pancreatic diabetes is the prototype, there are many other conditions producing the same end result but engendered by wholly different causes and operating under wholly different laws. The end result of glucose in the urine is the only point they have in common.

## PART II.

### CLINICAL SECTION

*Introduction.* Although the differential diagnosis of endocrine and non-endocrine conditions usually depends upon laboratory findings for its confirmation, the attempt of the clinician should always be toward simplification, since in many instances there is neither time, money, nor facilities for an elaborate study of the patient presenting an obscure disease picture. It is under such conditions that so much "experimental" endocrine therapy is employed, to the detriment of that branch of medicine and often to the patient. Therefore the present analysis was undertaken to determine what symptoms and signs are significant in separating endocrine from non-endocrine conditions, and to what extent that differentiation may be made without the aid of laboratory examinations.

It is well perhaps to state at the outset that so far as differential diagnosis is concerned, the non-endocrine conditions which have come to us for metabolism studies may be separated into two groups: namely, those in which the history and a careful physical examination disclose a typical picture, and those in which the history does not indite one organ or system and the physical examination is significant, largely because it affords only "negative" or non-specific evidence. In the former group, laboratory examinations may furnish corroborative evidence in regard to diagnosis, and valuable aid in treatment, but they are not essential for the identification of the disease present; while in the latter group, laboratory tests must be relied upon, in the present state of our knowledge, to disclose the facts by means of which the diagnosis is reached. For example, disease of the heart, or circulatory system, can almost always be satisfactorily diagnosed by means of the patient's story and the clinician's examination, and while electrocardiograms, blood pressure measurements and radiograms of the

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\*A paper is shortly to appear treating this matter in detail.

heart may furnish comforting assurance that the diagnosis is correct, they seldom modify it or the treatment essentially. In contrast, in primary anaemia, diabetes, asthma, syphilis often; and disorders of metabolism practically always, the laboratory evidence is necessary if the diagnosis is to be certain and treatment effective.

In this section, therefore, emphasis is placed on diseases of the latter group, since they are the ones most often confounded with one another. It is not often, in our experience, that infectious endocarditis and thyrotoxicosis are confused; the difficulty, as judged by the character of the patients referred to us, lies in separating neuroses of neurogenic origin from those secondary to metabolic disturbances, or in recognizing tertiary syphilis, early lesions of the central nervous system, anaemias and leukaemias as the cause of the patient's condition. The diseases which are most frequently confused with endocrine disorders may be found in table (I) (v. s.) which comprises a diagnostic grouping of the patients examined by us who showed no convincing evidence of endocrine disorder but in whom evidence of other functional disturbance or organic disease was found.

The table shows that the principal non-endocrine conditions encountered were, in their order of incidence, lesions of the central nervous system, cardiovascular diseases, psychoneuroses, deafness, chronic infections, and syphilis. The high incidence of vascular disease and deafness in this group is artificial, due to factors already pointed out.

A more exhaustive analysis of the diagnostic groups remaining serves to show why they are frequently mistaken for endocrine disturbances. Thus, of the central nervous system lesions, the greatest number were post-meningitic or post-encephalitic arrests of development, with a lesser number of epileptics and patients with the Parkinsonian syndrome. The differentiation between post-meningitic or post-encephalitic arrests of development and those due to mild thyroid failure, is from clinical evidence alone, often impossible, and since the former conditions are almost irremediable and the latter responds dramatically to treatment, it is only proper to give the patient the benefit of any existing doubt, and to determine, by means of such laboratory investigations as are necessary which condition really exists. So far as epilepsy and paralysis agitans are concerned, their frequent occurrence in our series is due not to mistaken initial diagnoses but to a commendable effort to detect, if possible, a curable cause for the symptom complex presented. In epilepsy, our studies have occasionally brought to light some associated disturbance of metabolism, the correction of which has resulted in an arrest of the convulsions, while in the case of Parkinson's syndrome they have served to disprove the theory that the condition is in some way due to "hypoparathyroidism."

Under the heading "psychoneuroses" are included neuroses and psychoses as well as true psychoneuroses. Whether or not the patients were correctly allocated to their proper sub-group, it is a significant fact that the symptoms were no more varied or severe in these "non-endocrine" patients than in those showing incontrovertible evidence of associated endocrine dis-



turbance (1, 2). We have been forced to conclude that every patient exhibiting symptoms of neurosis, psychosis or psychoneurosis deserves a careful medical endocrine study before the condition is ascribed to "neurogenic" or psychogenic causes. We do not wish to be understood as ascribing every neurosis or psychosis to disturbed endocrine function: but we do wish to emphasize the point that only by careful metabolic studies can such a condition, either associated or causal, be eliminated in case of any given patient.

In the group of the chronic infections, tuberculosis heads the list. Little comment is needed on this point. The difficulty of differentiating incipient phthisis from thyrotoxicosis has been pointed out by many writers, but it needs repetition in these days of diagnosis by means of a single basal metabolic rate to the exclusion of repeated physical examinations. It is perhaps significant that focal infections, not associated with disturbed metabolism, are so rare in our series. Attention has already been called in our papers on thyroid ovarian and pituitary disturbances, to the high incidence of focal infections in association with those conditions: the material presented here tends to support by its negative character our suggestion that focal infection certainly, at times, produces its deleterious effects via the endocrine system.

The presence of a large percentage of syphilitics in a series of patients suspected of endocrine malfunction is to be expected, and serves to illustrate the protean character of lues. It serves also to make clear the necessity for serological tests on all patients suffering from obscure conditions.

One other group of patients deserves comment here, that labeled in the table "disorders of metabolism." Though less important, numerically, it comprises two conditions often wrongly charged against faulty endocrine function, "malnutrition" meaning underweight, and obesity. Our studies of these patients confirm the opinion of other writers that in by no means all obese patients can a metabolic disturbance be demonstrated and to a certain extent controverts the theory frequently encountered that a pluri-glandular preparation is a good "tonic" for any individual who is underweight.

To summarize briefly the conclusions to be drawn from Table I, it may be said that, in considering the possibility of disturbed endocrine function in any patient, tuberculosis, syphilis, sequellae of meningeal infections, and "idiopathic" malnutrition and obesity must be ruled out by adequate objective evidence, while the possibility of disturbed endocrine function as a contributing or causal factor exists in any case of epilepsy, neurosis or psychosis, a possibility demanding adequate objective evidence for its proper evaluation.

An analysis of the histories and physical examinations of patients in the non-endocrine group justifies our emphasis upon the importance of the clinical examination of the patient, since it reveals certain facts which are of considerable help in separating, at least tentatively, the "endocrine" from the "non-endocrine" individual. This, although we believe that in

the majority of instances the clinical evidence must be substantiated by correlated laboratory tests before the examiner can properly treat the patient with an endocrine preparation. It must be recognized that many individuals can be spared the expense and bother of metabolism studies if the examiner gives sufficient time and thought to the results of his personal examination. A brief discussion of the most important clinical findings in this series is therefore necessary.

TABLE IX  
FAMILY HISTORY

Malignant .....	19.6%
Diabetes .....	7.0%
Thyroid Disease.....	3.0%
Tuberculosis .....	18.0%
Mental Disease.....	8.0%
Epilepsy .....	0.6%
Venereal Disease.....	1.0%
Blood Diseases.....	1.8%
Cardio-Vascular Diseases.....	13.8%
Disease similar to that of Patient.....	19.2%

*Inheritance.* The importance of inheritance in determining a patient's tendency toward certain diseases is still a matter of argument. With the growth of laboratory methods of diagnosis the "family history" was at one time almost disregarded, but more recent opinion seems likely to give it a place of considerable importance as an aid to diagnosis. Familial tendency to endocrine disorders is generally recognized, and our own studies (g. v.) furnish evidence in support of this idea. They also indicate that this familial tendency is more marked in endocrine than in non-endocrine diseases, since in the former there is a "positive" family history in approximately 40 per cent of the cases, while in only 19 per cent of the latter group was there a history of a near relative who suffered from the same disease as did the patient. These figures are not quite comparable since the term "endocrine disorders" embraces a large number of clinical conditions, but the preponderance indicates that careful inquiry into the patient's family history is likely to furnish evidence valuable enough to justify the effort involved. It should be pointed out, however, that the inheritance is not always specific. The fact that a parent or sibling has thyroid disease is no evidence that the patient's symptoms are due to abnormal function of that gland, but does furnish strong presumptive evidence that they may be associated with some endocrine disorder, if no organic pathology is found to explain them.

*Sex.* As regards this factor, our figures do not support the thesis that the female sex is peculiarly liable to endocrine diseases. Practically all of the gonad subjects (95 per cent), 73 per cent of our patients with thyroid disease and 60 per cent of those with pituitary disorders were females, but the possible significance of these figures is nullified by the fact that 63 per cent of our patients with non-endocrine disorders were also

females. The only conclusion justified by these findings is that, for reasons not pertinent to this study, women predominate in hospital clinics, and that in our material, the percentage of males with endocrinopathies was not significantly smaller than that with non-endocrine disease. We believe that endocrine disturbances are more frequently encountered in men than is generally supposed.

TABLE X

Diagnostic Group	AGE YEARS							Aver.
	1-10	11-20	21-30	31-40	41-50	51-60	over 60	
Infections . . . . .	0	6	10	14	15	11	0	38
Psycho-Neuroses. . . . .	1	3	22	14	11	6	3	36
Lesions of Cent.								
Nervous System . . . . .	8	18	26	12	11	4	3	29
Metabolism . . . . .	1	6	9	8	5	1	5	35
Cardio-Vascular.. . . .	1	6	9	11	11	8	15	44
Blood . . . . .	0	2	2	2	2	6	3	46
Tumors . . . . .	1	0	8	2	5	1	3	37
Syphilis . . . . .	2	9	6	11	7	4	4	35
Eye . . . . .	0	0	1	0	1	1	2	50
Ear . . . . .	1	8	22	12	10	3	1	33
Skin . . . . .	1	3	7	2	0	4	0	31
Gastro-Intestinal . . . . .	0	1	3	1	5	0	0	34
Pelvic . . . . .	0	0	2	3	0	1	0	34
Asthma . . . . .	0	2	0	1	4	2	2	44
Misc. . . . .	0	0	0	0	1	1	0	49
Normal . . . . .	2	2	5	4	3	1	1	30
Total.....	18	66	132	97	91	54	42	36
Per Cent.....	3.6	13.6	26.4	19.4	18.2	10.8	8.4	

*Age.* On the basis of division by decades, there is no significant difference in the age incidence of endocrine disturbances and those non-endocrine conditions which are most frequently confused with them. All

TABLE XI

## MARITAL HISTORY AND FECUNDITY

Diagnostic Group	Married		Dur. Av.	Concep- tions	Chil- dren	Mis- car- riages	Abor- tions	Infertile	
	No.	%						No.	%
Infections . . . . .	32	57	16	74	63	11	0	5	16
Psycho-Neuroses . . . . .	31	52	13	60	44	11	5	9	29
Cent. Nerv. System. . . . .	30	37	14	60	47	12	1	12	40
Metabolism . . . . .	17	49	19	48	28	19	1	5	29
Cardio-Vascular . . . . .	39	64	22	125	99	15	11	5	13
Blood . . . . .	12	71	25	31	24	7	0	3	25
Tumors . . . . .	10	50	12	12	10	2	0	4	40
Syphilis. . . . .	21	49	17	68	52 <sup>h</sup>	15	1	9	43
Eye . . . . .	4	80	31	15	14	1	0	0	0
Ear . . . . .	18	32	13	30	27	3	0	5	28
Skin . . . . .	3	18	17	9	8	1	0	0	0
Gastro-Intestinal . . . . .	5	50	9	10	8	1	1	1	20
Pelvic . . . . .	5	83	12	11	9	2	0	2	40
Asthma . . . . .	6	55	23	14	10	4	0	2	33
Intoxications . . . . .	2	100	23	8	4	1	3	0	0
Normal . . . . .	7	39	12	18 <sup>†</sup>	9 <sup>†</sup>	5	1	2	29

\*One with 15 and one with 10; remaining 19 had only 27 children.

†Three pregnant.

are characteristically diseases of adolescence and early adult life, though no age period is free from them. A few of the non-endocrine groups such as that of cardiovascular disease show some deviation but are not those in which confusion is most likely to occur.

*Fertility.* A study of sterility in "endocrine" and "non-endocrine" patients brings to light some interesting facts. Of our "non-endocrine" patients 26 per cent of the matings were infertile, as compared with 39 per cent in the thyroid, 36 per cent in the pituitary and 41 per cent in the ovarian group, evidence that a history of sterility is an important suggestion of endocrine disturbance. Further analysis of the non-endocrine group shows that the conditions most frequently associated with sterility include two which are difficult to differentiate from endocrine disorder, syphilis with 43 per cent and lesions of the central nervous system, with 40 per cent infertile. The only other conditions showing the same incidence of putative sterility are pelvic disease (40 per cent), tumors, benign and malignant (40 per cent) and asthma (33 per cent). The coincidence of pelvic disease and syphilis with sterility is well known and easily understood; that of asthma, tumors and central nervous disease we believe has not been previously recognized, and we have no explanation to offer for our findings. From the point of view of internist, obstetrician and gynecologist, however, it is important to realize that in searching for the cause of a sterile mating, a possible endocrine factor must be considered as important as any other single cause.

TABLE XII

## CATAMENIA

A. Onset	Before 12 22	12-14 212	After 14 65	Total 299
B. Period	Diminished	Flow Normal	Increased	Total
Irregular 85				
Diminished .....	7	16	11	34
Both .....	2	4	3	9
Increased .....	15	17	10	42
Total .....	24	37	24	85
Regular 214.....	41	138	35	214
Grand Total.....	65	175	59	...

*Catamenia.* Seventy per cent of our female patients in the non-endocrine group began to menstruate between their twelfth and fourteenth years, as compared with 45 per cent of the "thyroid group" and 65 per cent of the "pituitary group." In other words, non-endocrine diseases do not, in the majority of girls, cause significant delay of the menarche; but do cause such delay in over half of those with thyroid failure and in approximately one-third of those with disturbed pituitary function. These figures naturally derive from groups composed, in significant measure of women whose endocrinopathy was present during the years of maturation. In certain much larger series compiled by one of us (A. W. R.) the differences are less striking, but in each of these were a large number of women

whose history and physical evidences indicate an inception of the endocrine condition, years after the transition to maturity had taken place. In these larger groups, the ovarian cases show by far the largest proportion of women maturing within conventional normal limits, a possible indirect evidence either of the lesser part played by the gonad before maturity or equally to be interpreted as a lessened incidence of lowered glandular activity in the prepubertal years. Though the absolute figures differ, practically the same ratios hold for physical development in general, as indicated by abnormal weight and height, while the incidence of delayed mental development was practically the same in endocrine and non-endocrine conditions. As far as our evidence goes, arrested or delayed mental development is as often due to meningeal infections or birth trauma as to disturbed function of the glands of internal secretion. Over 70 per cent of the non-endocrine group show regularity of the menses, while the endocrine groups show a definitely lower incidence. The pituitary and ovarian cases show a tendency toward a lengthened interval while the thyroid group contains from four to five times as many women with complete irregularity as do any of the others.

The normal amount of the flow is somewhat elastic in its definition. Making due allowance for this fact, however, we find that while all of the groups show 50 per cent or more falling inside conventional limits, the division of the remainder between flow that is "scanty" and that which is "profuse" approximates a parity in every instance.

TABLE XIII  
AGE OF ONSET OF CHIEF COMPLAINT

Period	Incidence			
	Non-Endocrine	Pituitary	Thyroid	Gonad
0-10 .....	14%	2%	2%	9%
11-20 .....	24%	30%	19%	32%
21-30 .....	20%	22%	20%	31%
31-40 .....	18%	17%	17%	16%
41-50 .....	13%	20%	17%	7%
51-60 .....	7%	8%	18%	3%
Over 60.....	4%	1%	7%	2%

DURATION, NON-ENDOCRINE

Less than 1 year.....	12.8%
From 1 to 5 years.....	43.4%
From 6 to 10 years.....	20.8%
Over 10 years.....	23.0%

*Age of Onset and Duration of Chief Complaint.* The statements from which the above data derive are a somewhat uncertain quantity in which a subjective element is or may be dominant. For example, the high degree of incidence shown in the first three decades in the ovarian cases may be a real datum or no more than an expression of the ego centricity of the sufferers from this particular disorder. Barring the relatively high value for the incidence during the first decade in the patients forming the non-

endocrine group, the major sections show a definite degree of correlation with those of the pituitary series. The gonad cases concentrate in the first three decades, while those patients presenting thyroid disease show a substantially constant recognition with low incidence only in the first and last stadia. In the light of the subjective element, it is hard to say how meaningful these figures may be. With the large percentage of normal catamenial histories in the ovarian group, the fact that two-fifths of them date their chief complaint from the first two decades, engenders a certain scepticism. The 14 per cent in the first decade of the non-endocrine cases undoubtedly arises in the large number of young patients with disorders

TABLE XIV

## PAST HISTORY

Measles .....	83.8%
Mumps .....	48.2%
Chicken Pox.....	47.4%
Whooping Cough.....	59.4%
Scarlet Fever.....	26.2%
Diphtheria .....	16.6%
Typhoid .....	9.0%
Malaria .....	3.4%
Pneumonia .....	13.6%
Influenza .....	29.8%
Rheumatic Fever.....	3.2%
Arthritis .....	5.4%
Tonsil or Sinus, Infections.....	9.8%
Venereal Infections.....	7.8%
Nervous Diseases.....	3.0%
Encephalitis .....	3.4%
Renal Disease (acute).....	1.2%

## OPERATIONS

Tonsil and Adenoids.....	35.4%
Sinuses .....	3.0%
Infected Glands.....	4.6%
Eyes .....	3.6%
Nose .....	10.0%
Hernia .....	2.0%
Appendix .....	20.4%
Gastro-Intestinal	
Ulcers, etc. 2.2 }	
Gall Bladder 3.0 }	8.4%
Haemorrhoids. 3.2 }	
Tumors .....	3.8%
Pelvic	
Dilatation and Curettage 12.3 }	
Repair and Suspension 5.4 }	28.8%
Ovariectomy (one) 6.0 }	
Hysterectomy 3.8 }	
Caesarian Section 1.3 }	
Joint and Spine.....	5.4%

affecting the nervous system who were referred for the possible existence of a causal endocrine factor. This magnitude compared with the proportion of children in the pituitary and thyroid groups may offer a first rough approximation of the relative causation of physical or mental retardations.

The period of duration in the non-endocrine group does not differ substantially from our records in the endocrinopathies. This factor, like the

TABLE XV

## COMPLAINTS

	Chief (as given by patient)	Combined Primary and Secondary
Headache .....	10.2%	57.6%
Vertigo .....	4.2%	30.0%
Fatigue .....	24.0%	36.8%
Faintness .....	3.4%	10.6%
Convulsions .....	4.2%	5.6%
Nervousness .....	9.6%	27.4%
Pain .....	16.0%	30.8%
Paralyses .....	3.6%	
Tremors .....	2.2%	
Mental Disturbances.....	5.0%	
Underweight .....	2.0%	
Overweight .....	5.8%	
Disturbances of the		
Eye .....	4.4%	
Glasses .....		55.4%
Pain .....		8.4%
Poor vision .....		16.2%
Visual aberrations.....		13.6%
Ear .....	14.0%	
Ache .....		11.4%
Deafness .....		28.6%
Tinnitus .....		17.6%
Nose .....	1.0%	
Colds (frequent).....		22.2%
Catarrh (chronic).....		7.0%
Epistaxis .....		7.0%
Discharge .....		5.4%
Obstruction .....		9.0%
Mouth (canker).....		4.0%
Teeth		
Poor .....		18.2%
All extracted.....		10.4%
Throat		
Sore (frequent).....		30.0%
Cardio-Respiratory System.....	5.6%	
Dyspnoea .....		35.2%
Palpitation .....		28.0%
Pain .....		17.4%
Cough .....		19.8%
Cardio-Vascular System.....	11.8%	
Gastro-Intestinal System.....	11.6%	
Nausea .....		21.4%
Vomiting .....		18.2%
Pain .....		15.8%
Jaundice .....		6.6%
Constipation .....		41.2%
Diarrhoea .....		4.0%
Poor Appetite.....		31.4%
Genito-Urinary System.....	2.8%	
Frequency .....		15.2%
Nocturia .....		19.8%
Urgency .....		5.2%
Dysuria .....		7.8%
Menstrual Function.....	6.0%	
Delayed Onset.....		21.7%
Irregularity .....		28.3%
Dysmenorrhoea .....		24.7%
Skin .....	4.6%	
Arthritis .....	5.4%	
Paraesthesias .....		17.6%
Ataxia .....		3.8%

age of onset, is influenced unduly by non-controllable influences. We offer them as the opinions which they are, not as facts.

*Previous Illnesses.* The one outstanding feature in this table is the significantly greater incidence of tonsillar infection in the endocrine than in the non-endocrine group. Judged by the same standards, the former showed about 75 per cent with convincing evidence of present or past tonsillar infection, the latter, 45 per cent. We have called attention to the possible relation of chronic tonsillar infection to endocrine disease in previous papers (2) but the findings become doubly significant in the light of our present records. It is probably also significant that while the number of tonsillectomies previously performed was not significantly different in the two main groups, the incidence of unrecognized tonsillar infection was much greater in those with endocrine disturbance than in that with non-endocrine disease. At first thought this findings may seem paradoxical, but we believe that the explanation is that constant absorption from the unrecognized chronic tonsillar infection may be a potent cause of deranged endocrine function in any individual with an inherited predisposition of those organs. As a corollary, we believe that failure of the patient's general condition to improve following removal of definitely infected tonsils in every instance should raise the suspicion of a residual endocrine disturbance.

No other diseases in the patients' past histories show any particularly significant variation in incidence in the various groups studied; in fact, the percentage of occurrence of illness other than focal infection is almost identical for endocrine and non-endocrine groups.

*Present Illness. Exhaustion.* As has been pointed out in a previous paper, the characteristic symptom of thyroid disturbance is exhaustion or easy fatigability, and in this particular it differs from other endocrine and from the non-endocrine group in striking fashion. Fifty-nine per cent of our patients with thyroid disorder gave abnormal fatigue as their chief complaint, and it was mentioned as a marked symptom by an additional 21 per cent. The only other group in which it occurs in anything like such proportions is that of Addison's disease, and in this the condition is more properly described as asthenia, since there is a sense of physical weakness rather than the loss of energy which characterizes thyroid disorders. This energy deficiency was a chief complaint in 36 per cent of both the pituitary and ovarian groups, but in only 24 per cent of our non-endocrine patients, and was mentioned as an important symptom by only 13 per cent more. There are, however, certain sub-groups among the non-endocrine conditions in which the incidence of exhaustion approaches that of the thyroid diseases. These are the nervous disorders, neuroses, psychoses and psychoneuroses and the anaemias. These latter conditions indeed offer the greatest difficulty of differentiation from the endocrine groups, and correct diagnosis demands great care in evaluating clinical signs and laboratory findings. The presence of an anaemia, for example, does not rule out thyroid hypofunction, since the former is often due to



the latter; nor does a moderate depression of basal metabolism in a neurotic patient prove the existence of an endocrine disorder. It may be, and in a significant number of our patients was, due to nitrogen starvation. Likewise exhaustion may be caused as surely by emotional conflict as by metabolic deficiency, so that it often requires nice judgment and all the differentiating evidence available to determine whether a given patient is exhausted and nervously unstable because of a metabolic error, or from an emotional state which has as one of its results an insufficient food intake.

*Abnormal Weight.* There is a widespread tendency at present to connect overweight with endocrine disturbance, and to overlook its possible relation to underweight. The theory that overweight is due to hypofunction of some gland of internal secretion has received enthusiastic support from patients wishing to reduce, as it seems to offer them a method of accomplishing their purpose without self-denial. The result has been the injudicious use of thyroid extract or pluriglandular preparations as an adjunct to, or substitute for, dietary restrictions—a practice with dangerous possibilities. As has been pointed out by one of us (31), if the basal metabolism is normal thyroid extract reduces weight only when it produces toxic effects. Furthermore, our figures, and studies by others (32), do not indicate that overweight is in any sense pathognomonic of endocrine disorders. Only in disturbances of pituitary function is there found an exception to this rule. In the thyroid group obesity was the chief complaint in 8 per cent; in the ovarian, 10 per cent; as contrasted with 6 per cent of the non-endocrine patients, an entirely insignificant difference. The subjective character of such a chief complaint as obesity is emphasized from the following.

TABLE XV-a

Gland	Thyroid	Gonad
Per cent above predicted weight.....	60	51
Average overweight.....	+27%	+22%
Obesity as chief complaint.....	8%	10%

In these same groups, significant underweight was nearly as common as overweight. In short, our studies lend no support to the use of endocrine preparations in the treatment of obesity, as such, and rob it of any valuable significance in the differential diagnosis of endocrine and non-endocrine disorders.

*Headache*, of more than occasional frequency, was the chief complaint in 10 per cent of this series, and was about equally distributed among the various subgroups. As a definite symptom its occurrence was slightly greater among the non-endocrine than in any of the endocrine groups, a fact which is of significance in indicating the variety of factors causing this symptom and in minimizing its diagnostic significance. There is, however, some suggestion that headaches of the true migrainous type are

more frequently associated with endocrine disturbances than with organic disease.

*Nervous Instability.* "Nervousness" was the presenting symptom in 9 per cent of the group under discussion, in 8 per cent of the thyroid disturbances, and in none of the patients with pituitary disorders. In the ovarian cases it was frequently mentioned but usually as a secondary matter. It is a striking fact that nervous instability, so characteristic of lowered ovarian function, as possibly evidenced during the menopause and, in a different manner, in thyroid disorders, is conspicuous by its absence in the patients with pituitary disturbance. No explanation of the fact is at present available, and the presence or absence of "nervousness" is hardly a dependable differential symptom. It may be stated, however, that its presence as a definite symptom should logically raise the question of an underlying metabolic error as its cause.

*Vertigo* was not a frequent chief complaint in our "non-endocrine" patients, but demands discussion because of its serious import when it is an outstanding symptom. Drury's recent paper (33) discusses it in detail but it needs to be emphasized that from the internist's point of view, vertigo demands a careful search for organic disease of the central nervous system as the first step in the diagnosis. To this end, ability to use the ophthalmoscope and a reasonable experience in interpreting its findings, is essential to every internist and general practitioner.

As compared with our endocrine patients, the incidence of vertigo as a presenting symptom is greater in the pituitary group and not significantly different in any of the others. As a definite but secondary symptom it is surprisingly frequent in thyroid disturbances, and in them, was occasionally so severe as to simulate closely an intracranial tumor. In the ovarian group, its incidence was trivial. Neither the character nor severity of a vertigo, therefore, is sufficient to define its cause in all cases, and the possibility of an endocrine etiology must always be kept in mind while examining a patient with that complaint. Such a possibility should not, however, be entertained until lesions of the central nervous system have been rigorously ruled out.

*Menstrual Disturbances* were not frequent among our "non-endocrine" patients, occurring in only 6 per cent of this series, although from 25 to 30 per cent reported dysmenorrhoea and irregularity. These figures are in striking contrast to those for the thyroid and pituitary groups, in which the incidence was 59 and 54 per cent, respectively, while the ovarian cases head the list with 14 per cent presenting this condition as a chief complaint and show, in addition, 42 per cent with irregularity and 68 per cent with dysmenorrhoea. Excepting demonstrable pelvic disease, the only non-endocrine diseases frequently associated with disturbed menstruation are tuberculosis, the anaemias and leukaemias, conditions which, as we have already pointed out, often closely simulate endocrine disorders. If these conditions be certainly eliminated, a study of endocrine function is indicated in any patient with disturbed menstruation, a fact emphasized

by Graves (34) and others. In the absence of definite pelvic disease, surgical treatment for menstrual disorder is justified only when a possible endocrine disturbance has been eliminated—not by one “basal” metabolism test, but by a careful survey of general and special metabolism, a fact not yet sufficiently appreciated by the medical profession as a whole.

TABLE XVI  
PHYSICAL EXAMINATION

Development		
Good .....	70.4%	
Fair .....	21.4%	
Poor .....	8.2%	
Nutrition		
Good (normal) .....	35.8%	
Overweight .....	23.6%	
Underweight .....	40.6%	
Skull Abnormalities.....		9.0%
Hair		
Scant on Vertex.....	12.6%	
Excess on Body.....	12.8%	
Abnormal Pubic Distribution.....	4.8%	
Eyes		
Pupillary Abnormality.....	7.2%	
Abnormal Reflexes.....	9.6%	
Strabismus .....	4.0%	
Nystagmus .....	1.6%	
Exophthalmos .....	1.2%	
Deafness* .....		20.2%
Nose		
Septum Deviation .....	13.8%	
Discharge .....	4.2%	
Tender over sinuses.....	2.0%	
Teeth		
Poor condition.....	38.2%	
All extracted .....	14.2%	52.4%
Doubtful Tonsils* .....		16.4%
Enlargement of Thyroid.....		10.2%
Chest		
Asymmetry .....	6.2%	
Earlier Rickets.....	2.0%	
Lungs		
Dullness .....	8.4%	
Abnormal Sounds.....	16.6%	
Râles .....	12.2%	
Heart		
Enlarged .....	5.8%	
Murmurs .....	15.6%	
Abnormal Rale.....	9.6%	
Abdomen		
Mass .....	1.8%	
Tenderness .....	15.6%	
Hernia .....	4.8%	
Fluid .....	0.8%	
Enlarged Liver.....		2.6%
Palpable Kidney.....		1.8%
Enlarged Spleen.....		1.2%
Genital Abnormalities.....		2.4%
Adenopathy		
Cervical .....	18.4%	
Axillary .....	2.2%	
Inguinal .....	6.4%	
Skin Eruptions.....		27.8%
Varicosities .....		8.6%

\*See report on special examination

TABLE XVI—Cont.

Spine		
Scoliosis .....	10.2%	
Lordosis .....	6.0%	
Kyphosis .....	3.0%	
Tenderness .....	5.0%	
Abnormalities of Extremities.....		25.4%
Neuro-Muscular		
Knee Jerks increased.....	11.4%	
Knee Jerks diminished.....	13.8%	25.2%
Other abnormal Reflexes.....	6.6%	
Romberg positive.....	4.2%	
Clonus positive.....	2.2%	
Misc. tests positive.....	2.4%	
Loss of sound conduction.....	1.6%	
Mental Abnormalities.....		16.0%

There is an unfortunate tendency to belittle the physical examination in these days of instruments of precision and laboratory diagnosis. Nowhere is this tendency more prevalent or fraught with greater danger than in the realm of endocrine disease. It is perfectly true that the physical findings alone seldom furnish evidence adequate for the identification of disturbed endocrine function but it is equally certain that omission of a most careful and complete physical examination has led, and will always lead, to disastrous mistakes in the interpretation of laboratory findings. Reference to the case protocols appended to this monograph will show that non-endocrine disease may simulate an endocrine disturbance in every detail but one, and that one will be found, frequently in the physical examination. This is especially true as regards diseases of the nervous system, the anaemias, tuberculosis and syphilis.

In these conditions, careful observation should elicit evidence at least strongly suggestive of organic disease, and such suggestions of endocrine disorder as are encountered should be disregarded until the examination is complete. The presence of thyroid enlargement, for example, is no indication of disturbed thyroid function, and if such significance be attributed to it, the examiner may easily overlook incipient tuberculosis, adenopathy suggestive of syphilis or leukaemia or may interpret parasthesias as suggestive of thyroid disturbance when they are in fact the early signs of a pernicious anaemia.

Even those findings which are ordinarily regarded as significant of endocrine disturbance must be regarded with caution, since all of them may be encountered in patients in whom, at the time of examination at least, no evidence of disturbed metabolism can be found. The fact that they may well be residua of previous endocrine disorder does not justify their acceptance as criteria of the present metabolic level.

An example of the danger of interpreting physical findings as diagnostic of present endocrine disturbance is afforded by obesity. Because many patients with thyroid or pituitary hypofunction are obese, there is a tendency to reason (?) that all obese patients are suffering from thyroid or pituitary failure, and to dose them accordingly, often with disastrous

results. That such a deduction is entirely fallacious is proven by the fact that practically a fourth of our "non-endocrine" patients were significantly overweight and that a considerable number of them had at one time or another been given thyroid, or other endocrine substance as a part of their reduction treatment. While obesity, especially if it be distributed asymetrically, may raise the question of endocrine disturbance, it certainly cannot be accorded any weightier significance.

Similarly, abnormal height can be suggestive only, and even thyroid enlargement and exophthalmos were found in patients in this series, the former in 10.2 per cent, the latter in 1.2 per cent. The incidence of tonsillar infection was significantly less in our "non-endocrine" than in our endocrine group, occurring in only 16.4 per cent of the former. Focal infection, therefore, occurring in patients complaining of symptoms suggestive of disturbed metabolism, on the basis of probability is suggestive of the presence of an associated endocrine disturbance, rather than an argument against it.

Disease in the heart and lungs was far more frequently encountered in our "non-endocrine" than in our endocrine patients. In the former, evidence of pulmonary abnormality was present in 37.2 per cent of patients while it was conspicuous by its absence in those showing significant metabolic disturbances. Cardiac disease was encountered in 31 per cent of our non-endocrine patients. The possibility of mild cardiac insufficiency as a cause for fatigability, vertigo, cold hands and feet, indeed for all the symptoms so commonly encountered in an "endocrine" history, must be constantly borne in mind.

Abdominal involvement would hardly seem to simulate endocrine disorders, yet 23 per cent of the patients in the series under consideration referred to as probably suffering from endocrine disturbance, showed evidence of definite intra-abdominal disorders, possibly overlooked and certainly discounted through over-enthusiastic attention to certain endocrine "stigmata."

It would also seem that evidences of disease of the central nervous system often fail to receive the consideration due them, as 25.2 per cent of our "non-endocrine" patients had abnormal knee jerks, 17 per cent showed other abnormal reflexes, and 22.4 per cent, irregular pupils, disturbed pupillary reflexes, nystagmus or strabismus. Once more it seems necessary to emphasize the point that the presence of any of these findings demands the abandonment of interest in endocrine function until proper examination has disclosed or eliminated disease of the central nervous system.

Apparently those conditions, especially in their early stages, are frequently confused with "functional disorders" since of the patients in this series submitted to complete neurological examination 61 per cent showed definite neurological conditions, and lumbar puncture gave "positive" results in 44 per cent of the patients upon whom it was performed.

TABLE XVII  
SPECIAL EXAMINATIONS

Observation	No.	No. +	% +
Audiogram .....	159	145	91
Bacteriological .....	40	8	20
Barany .....	84	18	21
Biopsy .....	5	5	100
Cardiac .....	125	41	33
Cardiogram (Electro).....	46	26	57
Dental .....	16	15	94
Endermal .....	28	15	54
Genito-Urinary .....	24	16	67
Laryngological .....	93	39	42
Liver Function.....	14	9	64
Lumbar Puncture.....	23	10	44
Lungs .....	36	15	42
Neurological .....	182	111	61
Orthopaedic .....	51	44	86
Otological .....	43	26	60
Pelvic .....	95	28	29
Psychiatric .....	46	43	93
Rhinological .....	93	35	38
Skin .....	25	23	92
Surgical .....	23	13	56

	Special Exam. (Eye)	323 Exam.
Abnormal		
Discs .....	43.7%	
Fundi .....	8.7%	
Pupils .....	10.2%	
Fields .....	43.0%	
Blind Spots.....	54.2%	

## ROENTGENOGRAMS

Part	No.	No. +	%
Skull .....	247	55	22
Sinuses .....	59	37	63
Teeth .....	57	39	68
Heart .....	181	39	20
Lungs .....	207	79	38
G. I. Tract.....	37	22	59
Gall Bladder.....	6	6	100
Graham .....	9	6	67
Kidneys .....	10	6	60
Joints .....	53	34	64
Spine .....	44	15	34

The entire list of special examinations found necessary in the study of these "non-endocrine" patients are enumerated above, and it is only possible to emphasize here those which we have found most often necessary. These comprise complete neurological examination, examination of the upper respiratory passages and appendages, the many forms of radiologic study, and ophthalmological examinations, the latter affording perhaps more valuable aid than any other single examination in the diagnosis of the more obscure conditions encountered in this series.

In conclusion, it seems worth while briefly to restate what we have learned from the study of our "non-endocrine" patients.

First. We believe that endocrine and non-endocrine conditions often simulate each other so exactly that only by correlating complete clinical and laboratory study is differentiation possible.

Second. When clinical examination discloses evidence of organic disease, it must take precedence over any evidences of metabolic disturbance in determining the diagnosis.

Third. While the history and physical examination are essential to the differentiation of non-endocrine and endocrine conditions, clinical examination is often insufficient for the establishment of a correct diagnosis, and must be supplemented by such laboratory studies as may be necessary to reveal the status of metabolic efficiency.

In a succeeding paper will be published a series of protocols of non-endocrine cases simulating endocrinopathies.

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# ENDOCRINE DISTURBANCES AMONG HIGH SCHOOL BOYS

## 1. ADIPOSO-DYSTROPHIA GENITALIS.

SHEPARD SHAPIRO, M. D.

During the past three years the Department of Health Education in the High School of Commerce of New York City has been conducting physical examinations of the students as a part of a health education program. As a result much has been accomplished in improving the health conditions of the pupils of this school through direct and personal education in hygiene. A summary of these activities is given in another publication (1). Many data have been collected in respect to the occurrence of various diseases among these pupils.

This paper deals with the endocrine disorders found among these high school boys. This subject is a very important one and merits more consideration than has been given to it in the past. There is notable lack of effort to discover and control such diseases early in life despite the fact that they are readily recognizable during the school ages. Moreover very little is being done by the Bureau of Child Hygiene to detect any of the defects in children in the high schools. In this city the task of making physical examinations of all school children devolves upon the Board of Health.

The treatment of endocrine disturbances later in life (with the possible exception of certain types of goiter) usually proves unsatisfactory. A program should be established to attack these diseases in their earliest detectable stages. The preliminary observations presented in this paper are published in the hope that the medical profession, educators, and those interested in child hygiene will take cognizance of this field of activity.

### MATERIAL

Up to the present time 1850 pupils of the High School of Commerce have been examined. The medical examinations were conducted by a group of physicians practising medicine in New York City. Their services are voluntary and for scientific purposes.

The 1850 boys examined varied in ages between 12 and 19. Among them, 50 were found to have endocrine disturbances. The outstanding defect of these boys was adiposo-dystrophia genitalis. Of the 50 cases discovered 48 (2.6 per cent of the total number examined) showed this type of disease. The remaining two had simple (adolescent) goiters. In this paper only the cases of Fröhlich's syndrome will be discussed.

I have carefully examined the 48 subjects of Fröhlich's syndrome. These studies were made at school in collaboration with the teachers. Frequent reference was made to records obtained in class work. In a small number



of cases consent was obtained from the parents for metabolic studies. These were conducted at my office and included blood sugar and basal metabolic rate determinations.

### OBSERVATIONS

The disease is characterized chiefly by: (1) fat dystrophy; (2) genital hypoplasia with absence or delay of secondary sex characteristics; (3) mental obtundity. All these are present in every case at sometime during the course of the disease but one or the other factor may be dominant.

The most striking feature in the present series is in the readjustment of the body incident to puberty and adolescence. During those periods the various elements of the disease tend to approximate normality. The symptoms do not all change simultaneously nor to equal degrees. In some cases I find that certain stigmata of the disease remain apparently unaltered.

The retarded mentality is the first element to emerge from the sub-normal state. In my series this had already occurred in 47 of the 48 cases studied. The exception is a boy 16 years old who showed no progress in his work and is grouped with the ungraded pupils of the school. He presents also adiposity and genital hypoplasia to a striking degree. His weight is 250 pounds (113.9 kgm.). The girdle and pectoral obesity are very marked, and his voice is high pitched. The testes are descended but the genitalia are infantile. No indication of secondary sex characteristics is discernible. During the two years that I have been observing this boy he showed no sign of improvement in any of these elements of the disease including his mentality.

The remaining 47 pupils on the other hand show improved mentality. They are able to maintain satisfactory averages in their class work. Their ages however vary from 2 to 3 years older than the average in their respective classes which signifies that they had been backward in earlier childhood and remain handicapped by reason of this. One of these boys now excels the average pupil. During the past year he attained 90 per cent in mathematics and was among the leaders of his class in the other major subjects. This boy's mother stated that he had been noticeably backward in his childhood but that he has been rapidly coming to the fore during the past four years. He is now 16 years old and entering the third term of high school. But these changes are confined to his mentality only. The evidences of fat dystrophy and genital hypoplasia are still pronounced. (See figure 1.)

The fact that subjects of *dystrophia adiposo-genitalis* show rapid and progressive mental development between the ages of 12 to 16 deserves special emphasis. It is particularly important from a prognostic standpoint. The observations in this group of cases indicate that as a rule they are backward in earlier childhood but gradually emerge from this state so that by the time they reach high school age they are of average men-

tality. It is evident furthermore, that the view held by many observers that these subjects remain permanently retarded appears to be incorrect.

The psychic reactions of these boys to their physical conditions are of interest. Invariably I find evidences of self-consciousness about their unusual appearances. This has undoubtedly been aggravated by the frequent taunts of the other pupils following exposure in the swimming pool or in the shower rooms. As a result an inferiority complex develops in these boys. They seek to avoid attracting attention to themselves and consequently hesitate to participate in scholastic or extramural activities.

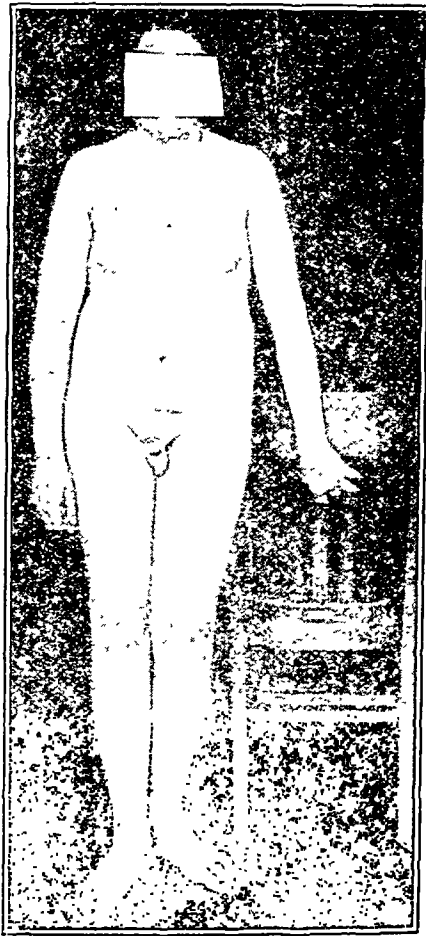


Fig. 1. Photograph of boy 16 years of age in whom the mentality has developed so that it even excels that of his classmates, but in whom the fat dystrophy and genital hypoplasia remain unchanged.

They do not mingle freely with boys of their own ages but choose as mates boys much younger than themselves. They tend to become introverts.

The hypoplastic genitalia may suddenly undergo maturation accompanied by the appearance of secondary sex characteristics. These changes occur less constantly and at a later age than the mental development discussed above but as far as I could determine may reach anatomical normality. Figure 2 is a photograph of a negro boy 19 years of age who gave a history of infantile sex development until the age of about 15

years. He now appears normal in this respect. It is interesting to note that this boy was mentally backward until his 12th year since which time he has progressed so that he is now an average student although 2 or 3 years older than the other members of his class. The fat dystrophy, girdle and pectoral obesity and large pendulous breasts are still pronounced and probably will remain permanently so.

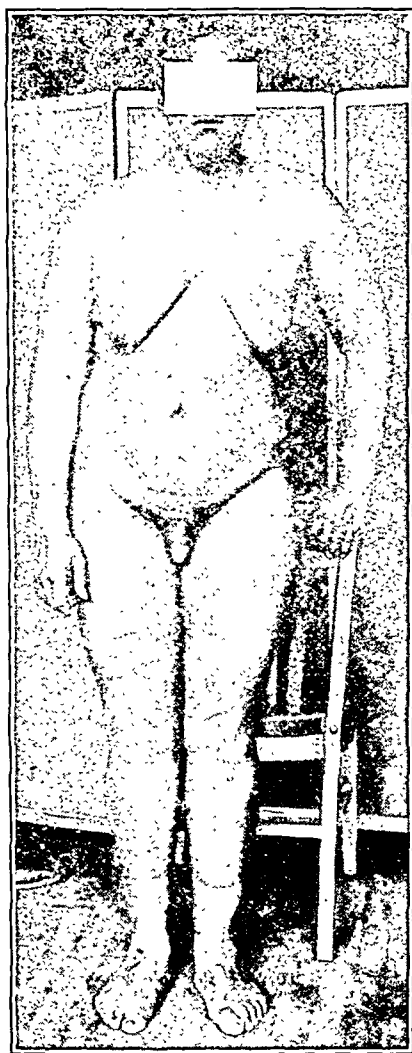


Fig. 2. Photograph of Negro boy, 19 years of age, in whom both mentality and genitalia have developed to normal, but in whom fat dystrophy persists.

The remaining defect, fat dystrophy, seems to undergo little change. It appears from older subjects which one sees in the clinic that definite remnants of this remain throughout life.

Actually very little is known of the nature of this fat dystrophy. The opinion has repeatedly been expressed that the excessive fat deposits result from increased storage of glucose and subsequent conversion of this into fat. Supporting this is the fact that these patients usually have in-

creased tolerance for carbohydrates. In this disease also, the basal metabolism is subnormal. These phenomena are akin to those operating in thyroid deficiency.

Individuals who have dystrophia adiposo-genitalis do not as a rule eat excessively. Nor do they have ravenous appetites for sugars. In spite of this they are obese and gain weight progressively. I do not favor the idea that the adiposity is a result of subnormal heat production (basal metabolism). The low findings obtained in these cases are possibly due to altered surface area consequent to the large deposits of inactive tissue. If these cases were calculated on the basis of ideal weight many would fall within normal limits. Furthermore Shapiro and Kliatsheo (2) demonstrated that in these cases the fat dystrophy may progress even in the presence of diabetes mellitus and subnormal carbohydrate tolerance. It is obvious from these controversial findings that there remains much to be demonstrated concerning the nature and genesis of the fat dystrophy in Fröhlich's syndrome and that any explanation of it at the present time would be purely speculative. My observations in the present series of cases demonstrate further that during the period the body is undergoing the readjustment incident to puberty and adolescence the fat dystrophy lessens in degree very slightly.

Considerable difficulty is encountered in attempting to treat these high school boys. Permission was sought from the school authorities and from the parents to treat some of these pupils by organotherapy. Unfortunately, however, with one exception, these parents have not been willing to cooperate with us. This part of the program is therefore deferred until a future time.

#### SUMMARY AND CONCLUSIONS

About 2.5 per cent of 1850 high school students are found to have endocrine disturbances.

Forty-eight out of the 50 cases discovered are diagnosed dystrophia adiposo-genitalis.

During the readjustments incident to puberty and adolescence the three predominating elements of the disease, fat dystrophy, genital hypoplasia and mental obtundity, are found to behave differently.

The mentality is the first to emerge from the subnormal state. The subject may recover entirely from this but remains permanently handicapped by virtue of his earlier retardation.

The hypoplastic genitalia may undergo rapid and progressive development eventually approximating anatomical normality. This takes place later and less constantly than the improvement in mentality.

The fat dystrophy shows only slight change.

I wish to thank Dr. E. J. McNamara, principal, and Dr. Michael Levine, of the Department of Health Education, of the High School of Commerce, for their willing cooperation in conducting this work.

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# MACROSOMIA ADIPOSA CONGENITA

A NEW DYSENDOCRINE SYNDROME OF FAMILIAL OCCURRENCE

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"It happens again and again that the hereditary peculiarities of the individual are revealed only by study of the progeny, nay, often only by observations on the third generation."—*W. Johannsen*: Heredity.

Very little is definitely known as to the physiological function of the adrenal cortex. We know, however, from the pathology that *lesions* in the cortical substance may considerably influence the general somatic as well as the genital development of the organism so that this will take quite a pathological course.

The theory of the cortical substance as an independent endocrine organ dates from the beginning of this century, when Linser presented his view as to the significance of the interrenal system to the normal development of the organism. A few years later the probability of this view was confirmed by Bulloch and Sequeira on basis of their pathologic-anatomical and clinical observations on a girl, who, at the age of 10 years, began to grow excessively, became very fat, and started to menstruate. In a short time her entire habitus was that of a preclimacteric woman. Autopsy revealed a tumor originating from the suprarenal cortex. None of the other endocrine organs showed any pathological condition. From the literature Bulloch and Sequeira gathered 25 similar cases, in the which cortical tumors had also been present. Thirteen of the subjects did not have any genital symptoms.

Another valuable contribution to the clinic of the suprarenal syndromes was later furnished by Guthrie and Emery, who pointed out that *excessive obesity* as a symptom in cortical tumors is just as dominant as are pathological conditions of the genitalia. On the basis of the observations by themselves and by others, these authors set up two main types of suprarenal syndromes:

1. The *obese* type and
2. The *muscular* type ("infant Hercules").

Guthrie and Emery give 10 instances of the obese type, 7 girls and 3 boys. Autopsy showed the presence of malignant cortical tumors in 6 of the girls and in 2 of the boys. In one girl all the endocrine organs were found to be normal. Autopsy was not made on one boy.

According to Guthrie and Emery the clinical features of the obese type are as follows: The children are puffy, with fat and pendulous cheeks which are the site of telangiectases. The skin is of a darkly congested color. Striæ distensæ may appear on abdomen and femora. Pan-*niculus adiposus* is strongly developed and usually distributed equally throughout, but the arms and legs may remain normal. The extremities are cool, cyanotic, and often the site of slowly healing ulcerations. The mammae are large and pendulous. The expression of such patients is mostly dull, melancholic, and at times suggestive of idiocy. In some instances these children are imbecile, but most often they are psychically ahead of their age.

*Abnormal hairiness* is met with in all instances of cortical tumor, either in the form of premature pubic or axillary hair growth or as a general hypertrichosis.

*Abnormal development of the genitalia* is not a conspicuous feature in children of this type. Such a condition, on the other hand, is *always present in the muscular type*, in which the most distinctive signs are universal athletic muscular development ("infant Hercules"), *pubertas præcox*, hypertrichosis, and premature ossification of the bones.

Among the cases reported, Guthrie and Emery found no instance in which the premature development was manifest before the age of 2 years; and in every child with one of the syndromes mentioned the childish facial expression had become grown-up and old-fashioned. Guthrie and Emery reach the conclusion that the presence of tumor-like conditions in the suprarenal cortex in children may give rise to two different types of precocity, namely, the obese type, which occurs in both sexes, and the muscular type, which is found in boys only. They add that premature, relatively abnormal, hirsutes is associated with practically every instance of premature development, though it is not necessarily connected with signs of sexual maturity.

The obese type is of greatest interest to our subject; and I shall illustrate the type by briefly abstracting a case as reported by Guthrie and Emery.

This patient was a boy who at the age of 3 years began to be increasingly stout. At the same time, hairs began to appear on pubes and the upper lip. When 5 years old, he resembled "a burly brewer's drawman" in miniature. His cheeks were enormous, of a reddish color from telangiectases. The shoulders, trunk and upper extremities were the site of voluminous fat accumulations. The mammae and the abdomen were bulging with fat. The lower extremities, however, were not particularly fat, but remarkably muscular. The hair on his head was particularly thick. The eyebrows were bushy and coalescent; the lashes long and heavy. Thick brown hair covered the back and pubes. There was an incipient mustache and beard. The development of the genitalia was in keeping with the age of the child. Intellectually he was ahead of his age, and he would make "shrewd and quaint remarks which showed considerable powers of observation." He died three months later from miliary tuberculosis. Autopsy revealed a walnut-sized tumor at the upper extremity of the kidney; microscopic examination showed the tumor to be a malignant neoplasm of the suprarenal cortex. The other endocrine organs appeared normal.

Guthrie and Emery do not attempt to give any detailed explanation of the *pathogenetic* connection between the pathologic-anatomical changes in the suprarenal cortex and the precipitate somatic development of the individual. Apert, on the other hand, divides the suprarenal syndromes into two groups according to the pathogenetic conditions he assumes to be present. One group covers the symptoms that are due to a *hyperfunction* of the cortex; the other group, the exact reverse, is made up by the symptoms that are due to a *hypofunction* of the cortical substance. Either of these conditions may, according to Apert, occur in adults as well as in children; but the clinical manifestation of such a functional disturbance will vary according to the age of the individual at the onset of the lesion. These differences, however, are not differences in quality, but merely in degree. Apert discusses in particular the influence of the cortical substance on the development of *heterologous sexual characteristics*, a question that is also considered by Guthrie and Emery.

Collett, Berner, Krabbe, and others have later made some valuable contributions to elucidate the relation between the interrenal system and the development of abnormal sexual characteristics.

The cortical hyperfunction corresponding to the cortical hyperplasia (syn. *Apert's hirsutism*, *Gallais' syndrome génito-surrénale*) is manifested, Apert states, by the triad: excessive obesity, hypertrichosis, and functional disturbances of genitalia; whereas hypofunction due to cortical hypoplasia is disclosed by: hypotrichosis, atrophy of the fatty tissue, and deficient somatic development (*senile nanism*, *progeria*). The cortical hyperfunction, which is most frequent in women, may occur at any age. The earlier its manifestation, the more definite are its symptoms. The aspects of the hyperfunction are most conspicuous when it sets in as early as the first embryonic period; for it will then result in *pseudohermaphroditism* (ovaries and uterus, panniculus, vaginal atresia, and virile secondary sexual characteristics). If the hyperfunction sets in during a later, foetal period, the secondary, heterologous sexual characteristics will be less conspicuous: the ovaries and uterus are atrophic, and there appears a universal hypertrichosis. If the cortical hyperfunction begins before puberty, it results in a premature somatic development with premature puberty, adiposity and hypertrichosis. After puberty the onset of cortical hyperfunction will result in obesity, menopause and hypertrichosis. The symptoms will be least pronounced if they do not develop prior to the climacteric period, as hypertrichosis then will fail to appear; obesity, however, and genital disturbances in form of metrorrhagia are present (Apert).

Gallais designates these results of cortical hyperfunction as *le syndrome genito-surrenale*. Collett has reported such a case of premature somatic development with hypertrichosis and virilism in an 18 months old girl. She weighed more than 15 kgm. (normal weight ca. 10 kgm.) and measured 81 cm. in length (normal length ca. 78 cm.). *The connection between the suprarenal cortex and the symptoms was obvious, as the*

*successful operative removal of a cortical tumor made the signs of premature development subside.*

Berner has reported an analogous case in an animal that is of the greatest interest to the comparative pathology. He demonstrated the presence of a malignant tumor, originating from the suprarenal cortex, in a virile *Leghorn hen* with marked arrhenoidism.

It should be mentioned, too, that Krabbe, who has made a valuable contribution to the explanation of the connection between heterologous sexual characteristics and the interrenal system, has reported a peculiar case of external masculine pseudohermaphroditism in a child of premature birth where one testis was replaced by a tumor consisting of suprarenal cortex cells. Krabbe's theory will not be discussed in this place, as it is of no direct import to the subject in question.

Thus Gallais, Apert, Collett, Berner, and other authors lay particular stress upon the genital abnormalities in lesions of the suprarenal cortex, whereas Bulloch and Sequeira and, especially, Guthrie and Emery emphasize that the general premature development with hirsutes and obesity is an equally distinctive phenomenon, and that the genital changes often are lacking altogether.

All authors, however, who have discussed the pathology of the interrenal system, are agreed that abnormal endocrine function of the cortical cells—whether due to simple hyperplasia, or to hypoplasia, to adenoma, or to malignant tumors—may have a pathological influence on the development of the body and genitalia so that this is accelerated, retarded, or modified sexually—according to the nature of the influence.

Opinions differ as to how this takes place. It seems most likely that the symptoms develop through a lack of endocrine coordination, which may be introduced by a dysfunction of the cortical substance, but is followed by a disturbance of the endocrine balance in such a manner as to influence, too, the secretion of other hormonopoietic organs (pluriglandular dyshormonism); these are not always, however, accompanied by any essential changes in the morphology of the secondarily affected endocrine organs.

There is, however, no absolute and unexceptional dependence of the abnormal somatic conditions on the cortical lesions mentioned. For, as is well known, it is only in a relatively small number of cortical tumors that we meet with a suprarenal syndrome; and, on systematic examination of the suprarenal glands, Keilmann found cortical adenomata in a great many children of perfectly normal somatic development. The reverse condition: a typical suprarenal syndrome without demonstrable pathologic-anatomical changes in the cortical substance may likewise occur. Guthrie and Emery report such a case, in which autopsy on a 3-year-old girl of the obese type showed perfectly normal endocrine organs.

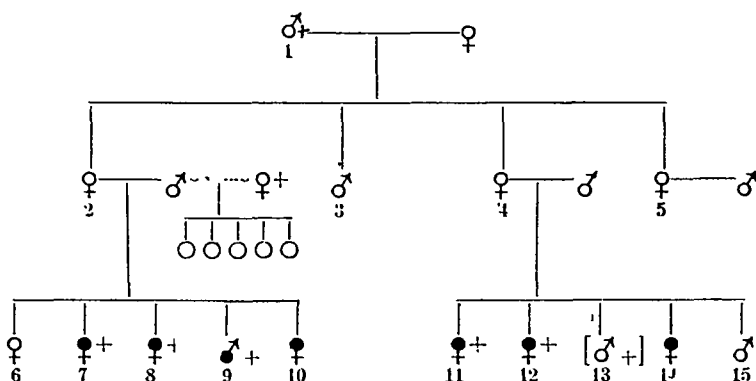
In turning to the subject, *Macrosomia adiposa congenita*, I shall first briefly outline the histories of the individual members of that family



in which I have observed this lesion (see the schema). The report is based partly on my own observations, partly on case-histories in Odense Hospital.

I have not succeeded in tracing the lineage farther back than to the grandparents of that generation in which the pathological individuals appear. But, as far as can be learned from the family members now living, *no adult* individual of this family has ever shown any sign of gigantism, stunted growth, obesity, acromegaly, or myxedema; nor idiocy, imbecility, or insanity.

#### SCHEMA OF THE FAMILIAL OCCURRENCE OF MACROSOMIA ADIPOSA CONGENITA



● = *Macrosomia adiposa cong.*

○ = normal.

+ = dead.

- No. 1. Maternal grandfather, normal. Died of pneumonia at the age of 62.
- No. 2. Normal woman, 32 years, with late menarche.
- No. 3. Normal man, 30 years.
- No. 4. Normal woman, 28 years, menstrual disturbances.
- No. 5. Normal woman, 25 years.
- No. 6. Normal girl, 7 years, small goiter.
- No. 7. Girl with cong. macrosomia. Died 9 months old.
- No. 8. Girl with cong. macrosomia. Died 4 months old.
- No. 9. Boy with cong. macrosomia. Died 10 weeks old from acute glossitis.
- No. 10. Girl with cong. macrosomia. *Living*, 18 months old.
- No. 11. Girl with cong. macrosomia. Died 3 months old.
- No. 12. Girl with cong. macrosomia. Died 6 months old.
- No. 13. Boy, born 2 months before term. Died 5 days old.
- No. 14. Girl with cong. macrosomia. *Living*, 4¾ years old.
- No. 15. Girl, normal, 2 years.

#### SUBJECTS STUDIED

No. 1 on the schema is the maternal grandfather of the abnormal individuals. He died at the age of 62 years. He was normal as to somatic and mental development, and showed no sign of endocrine disturbances. Autopsy showed acute pneumonia and chronic pulmonary tuberculosis.

His widow, the maternal grandmother of the pathological individuals, is still living. She is perfectly normal. Neither of these two grandparents has any hereditary defect, as far as is known. They were *not kindred*.

Their children, who form the next generation, are all living. They are one son and three daughters.

*No. 2.* The oldest one of these is a 32-year-old woman of middle size and normal appearance. Physical examination reveals no signs of endocrine disturbances, but she states that *her menses did not come on before she was 20 years*. The menses have always been regular and of normal type.

She married a healthy man, in whose family there has been no abnormality of any kind, and with whom she is *not kindred*, as far as they know. By this marriage she has been mother to 5 children (Nos. 6, 7, 8, 9, 10), of whom *no less than 4 are abnormal, suffering from macrosomia adiposa congenita. Only one of her children, No. 6, the oldest, is of normal development.*

By a previous marriage the father has 5 normal children. This is a point of interest with respect to heredity.

*No. 3* is a 30-year-old, single, farmer, of average height and size, and without any peculiarity.

*No. 4* is a 28-year-old woman, also of normal physique and normal mentality. Like her sister (*No. 2*), she has married a normal and *non-kindred* man, and she has been mother to several abnormal children (*3 out of her 4 children born at full term were suffering from congenital macrosomia*), and, besides, she too gave a history of menstrual disorders. Her menses began when she was 16 years old; they have always been of very short duration (2 days), very scanty and most irregular, with intervals as long as 6 months.

*No. 5* is a 25-year-old woman, perfectly normal in every respect, including the menses. She is married but has no children.

The succeeding generation comprises the abnormal children. As mentioned, this generation consists of two collateral branches: the children of the two above-mentioned sisters (*Nos. 2 and 4*). Here the morbidity is exceedingly high. *Among 9 children born at full term 7 were suffering from congenital macrosomia*, and only two of these are still alive (see the schema).

To make the aspects of congenital macrosomia as complete as possible, I shall now mention each of these children individually.

*No. 6* is a 7-year-old girl. The pregnancy and delivery were normal. She was breast fed. The somatic development was normal. She is bright and lively. On physical examination I found a very small goiter, but no signs of hypothyroidism nor hyperthyroidism. Nor did I find any sign of other endocrine disturbances.

*No. 7* is also a girl who was born at full term, by natural delivery after a normal pregnancy. She was already large at birth, but of normal proportions. She, too, was breast fed. Shortly after birth she began to grow enormously, as her length as well as her weight kept on increasing quite disproportionately; and at the age of 9 months she was "as large as a 4 years old child." Her appetite was ravenous. The urine output was excessive. She was very fat. One morning, when she was 9 months old, she was found dead in her bed, without having shown any sign of illness the preceding evening. The mother thinks that she was somewhat retarded mentally. There was no sign of premature puberty or abnormal hairiness.

*No. 8* was likewise born at full term and by natural delivery. She was a large child, even at birth. Shortly after birth she began to grow excessively, just like her preceding sister (of whom she was a true copy). She, too, showed an enormous general accumulation of fat. She died at the age of 4 months, likewise unexpectedly. The genitalia were of normal development. Her mentality was normal.

*No. 9* is a boy, born at full term, after normal pregnancy and by natural delivery. Like his sisters, he was large at birth and began at once to grow "beyond all measures." He died in Odense Hospital, of acute glossitis, when he was 10 weeks old. The *case-record* states that the somatic development of the child had been exceedingly rapid. He was fed at the breast, which he emptied with great avidity. He wet his diapers often and sweat considerably. His organic functions were normal. Mentally, he was ahead of his age. He could lift his head. He smiled and recognized familiar surroundings. One morning the mother noticed that his tongue rather suddenly became markedly swollen and that this swelling impeded the respiration to a large extent. The child was immediately admitted to the surgical department. On admission he weighed

6 kgm. (normal weight for his age ca. 4.5 kgm.) and measured 62 cm. in length (normal length ca. 55 cm.). The tongue was markedly swollen, especially at the root. He was foaming at the mouth. The swelling extended to both submaxillary regions. Auscultation of the lungs and heart indicated that these structures were normal. The thyroid was not palpable. The abdomen was normal. The testes, of hazel-nut size, had descended. There was no abnormal hairiness nor sign of premature puberty.

As the child was dyspnoeic and cyanotic, tracheotomy was performed at once and artificial respiration was attempted, but the patient died shortly after admission.

*Autopsy:* No hypertrophy of lymphoid tissue was found anywhere. The development and weight of the thyroid gland (10 gm.) corresponded with the age of the child. The parathyroid glands could not be demonstrated. The *suprarenal glands* were of normal shape and appearance, weighing 4 gm., corresponding with the age. The cut surface appeared normal. *Microscopic examination* showed mainly normal conditions; in particular, the cells appeared normal, as did the proportional amounts of cortex and medulla. The *cortical substance* contained several small adenomata. The chromaffin tissue along the aorta was well developed.

*Thymus:* The size, form, consistency, color, and weight (20.5 gm.) were normal and showed no definite abnormality microscopically; many Hassal's corpuscles corresponded with age of child, and a number of *eosinophile cells* diffusely and in groups along the vessels were seen. The testes were well developed, the size of a hazel-nut. The pancreas was apparently normal. The hypophysis was obtained only as formless tissue elements. The brain was very soft; the gyri and other outlines normal. There was no evidence of tumor, particularly in the hypophysis. The heart was normal (wt. 43 gm.). The liver and spleen showed no enlargement or other abnormality. The *tongue* was enlarged and firm; microscopic examination demonstrated glossitis.

These autopsy findings will be discussed later.

No. 10 is a girl, now *living*, with congenital macrosomia. At the age of 3 months she was admitted to Odense Hospital. At this writing she is 18 months old. She was born at full term, by natural delivery. Her weight at birth was 4 kgm. Like her sisters and brother, she began at once to grow excessively.

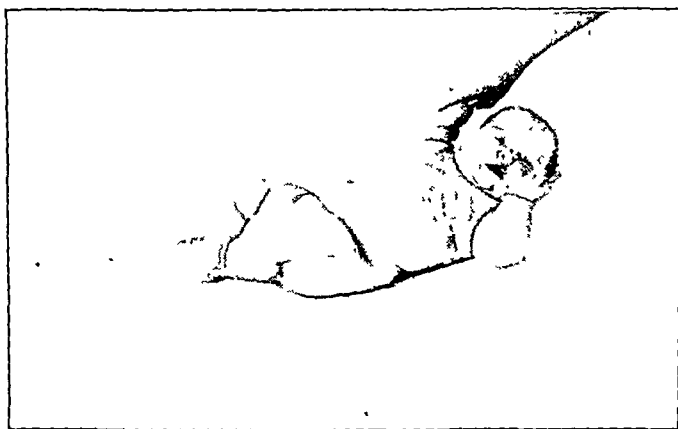


Fig. 1. Female patient No. 10 at the age of three months.

Her appetite was ravenous and she voided frequently. No excessive sweating, no cramps, and no tendency to spasmodophilia were noted. She is said not to have been somnolent. On admission to the hospital, when 3 months old, she was enormous for her age (see Fig. 1 and 2). Her length was 71 cm. (ca. 13-14 cm. more than normal). The proportions were normal, apart from the disproportionate general hypertrophy of the subcutaneous adipose tissue, which made the entire body surface—particularly on the femora—appear as large pillows separated by deep furrows. At that time she weighed 18 kgm. (!), that is about 14 kgm. more than normal for her age. The skin was normal throughout, espe-

cially without abnormal hair-growth. There was no sign of premature puberty. The genitalia were infantile female, with no sign of hermaphroditism. There were no tetanic or rachitic stigmata. The thyroid gland was not palpable. There were no glandular swellings. She had no teeth. She cried much; her voice was strong and piercing. Mentally she seemed ahead of her age. She would smile, pay attention and recognize. The eyes were normal. Auscultation of heart and lungs gave normal findings. The abdomen was fat and large, without sign of enlarged organs or tumors. Both fontanels were open; the anterior fontanel admitted a large finger-end, and was slightly tense.

*X-ray examination:* No definite abnormality of the skull and, in particular, no evidence of enlargement of the sella turcica were seen. The bones of the body were much further developed than normal in a child of that age. All the pelvic bones were large. Well-developed centers of ossification were present in both epiphyses of the femora and tibiae. There was a *definite center of ossification in the patella (!)*. There was no center of ossification in the head of the



Fig. 2. Same patient as Fig. 1, also at three months.

radius, but well-developed centers in the external condyle of the femur and the inferior extremity of the radius. Ossification of 3 carpal bones on both sides (among these, os triquetrum [!]) was present.

*Blood examination:* Smears, stained after Leishman, showed erythrocytes of normal shape, size and color affinity; no immature red cells; several myelocytes, but no myeloblasts. The *differential count* showed per hundred: 35 neutrophilic polymorphonuclear leucocytes; 8 eosinophiles; 13 myelocytes; 28 small lymphocytes; 9 large lymphocytes, and 7 transitional forms.

The urine contained no blood, pus, sugar, nor albumin.

The fasting blood sugar was 0.069 per cent.

The child was very greedy; she emptied her bottle avidly. She slept almost all the time between meals. In the sitting position she salivated a great deal; and she voided frequently.

*Summary:* In this series of 5 children, 4 individuals were suffering from *macrosomia adiposa congenita*. The oldest child of the series is normal with respect to somatic development, but has a small goiter. Only one of the pathological individuals, the youngest, is still alive (18 months old).

The other series, the children of No. 4, comprises also 5 individuals. This series, too, has included only one child of normal somatic development.

No. 11, a girl, was born at full term by natural delivery. She was large at birth; she began at once to grow enormously. She was breast fed. She presented exactly the same features as did the patients described above. She died unexpectedly, in 1920, at the age of 3 months, and from no demonstrable cause.

No. 12, a boy, took after his sister in every respect. He likewise died unexpectedly when 6 months old, after having grown enormously large and heavy. Neither these two nor any of the other children showed any sign of premature or heterologous development of genitalia or hirsutes.

No. 13, a boy, may be left out of this survey, as he was born 2 months before full term, and died when 5 days old. For the sake of completeness, it may be added that in this case the pregnancy was complicated by premature separation of the abnormally implanted placenta.



Fig. 3. Female patient No. 14 at the age of eight months.

No. 14 is a girl. As shown by her photograph (Fig. 3), she also suffers from macrosomia. She was born at full term, in 1923. She was admitted to Odense Hospital at the age of 8 months. She is *still alive*. Her history differs really in no particular from that of her abnormal sisters and cousins: she was large at birth and began at once to grow excessively. Before long she was immensely fat. She nursed with great avidity every 3 hours, and over 20 minutes each time. In addition, she got milk-food from the age of 7 months. She cried much and was very restless if she did not get her food "on the dot." Her psychic development corresponded with her age. *Dentition began at the age of 4 months.*

On admission to hospital, the child was enormously large and fat. Her length (8 months old) was 76 cm. or 10-11 cm. more than normal; the weight was 20 kgm., or about the weight of a normal 6-year-old child. As seen from her picture, her body-surface is made up of large pillows of fat separated by

deep furrows. There is no abnormal hairiness, no abnormal development of genitalia. Sweating and turgor of the skin were normal. She had a strong voice. The posterior fontanel was closed; the anterior fontanel admitted one finger. There was no sign of acromegaly, no goiter, no rachitic, or spasmophilic stigmata. Now she had 8 teeth. Auscultation of the heart and lungs gave normal findings. There was no enlargement of the abdominal organs and no tumor. Rectal exploration showed no abnormality. The hemoglobin was 77 per cent (Sahli). The urine was normal.

As mentioned, the child is still alive (Nov. 15, 1928). I examined her in June, 1927, when she was 3½ years old.

At that time she was still very large and fat, although to a considerably less extent than at her stay in hospital 2 years before. Now she weighed 22.4 kgm., or ca. 7 kgm. above normal. She is said to have lost a great deal of weight during the past 6 months and her craving for food has become less ravenous. She measured 97 cm. in length (7-8 cm. more than normal). All the teeth were present. There was no goiter, rachitis, hypertrichosis, or premature puberty. Mentally she is backward; she can say but a few words, and she is uncleanly.

It looks then as if the somatic proportions and further development are tending toward normality. Yet she still shows signs of congenital macrosomia with relative increase of the subcutaneous fatty tissue, but there is no doubt that the violent growth of her earliest months has subsided. Mentally, she is a backward child.

No. 15 is a 2-year-old girl, born at full term. Her physical and mental development are said to have been normal, and she shows no symptoms of macrosomia, obesity, premature puberty, or any other result of endocrine dysfunction.

*Summary:* This series that is made up by the children of subject No. 1, comprises 1 children born at full term, and 3 of these suffer from *macrosomia adiposa congenita*. In this connection, the prematurely born child, No. 13, is left out of consideration. One of the 3 abnormal individuals is still alive; she has now reached the age of 4¾ years. She is still suffering from macrosomia. Only one of these 4 children, the youngest, is of normal somatic development.

#### DISCUSSION

In surveying the histories given above, we find that the symptoms of the congenital macrosomia have been identical in all the patients; in fact, the resemblance of these patients is almost confusing. Symptomatologically, the 7 pathological individuals form a unity, and the manifestations of the abnormality are quite stereotypical, indicating a definite and uniform pathogenetic and etiological basis.

*Macrosomia adiposa congenita, which occurs in both sexes, is a constitutional anomaly of growth that is manifested soon after birth by progressive, premature, universal development of the soma—in such a manner, however, that an excessive, endogenous deposition of fat produces a disproportion between the height and the weight of the body.*

As to the skeleton, the excessive growth is evident from the increase in length as well as from the presence of premature centers of ossification and the premature dentition. The blood sugar percentage is normal. The urine contains no pathological substances. Relative eosinophilia has been demonstrated.

The increased diuresis may be explained by the copious intake of fluid—on account of the marked voracity of the children. As absolute measures

of the amount and the specific gravity of the urine are lacking, one cannot to a certainty exclude the possibility of a coexisting diabetes insipidus.

Another characteristic of these cases is *the low vitality* of these children and their lowered resistance to accidental injury, a fact that is met with in most dysendocrine conditions, particularly those associated with premature development (Biedl, Bell, Guthrie, Emery). Thus 5 of the 7 patients died in their first year of life.

As to the mental development, it seems as if such children may be ahead of their age, like the case reported by Guthrie and Emery and cited above. But, in case of No. 14 of this series, where known age ( $4\frac{3}{4}$  years) made a more exact judgment practicable, the patient was found to be intellectually backward.

The infantile aspect of these individuals persists in spite of the rapid development.

*The development of genitalia presents no abnormality*, especially as regards premature puberty and hermaphroditism.

*Turgor of the skin, sweat secretion and hairiness are normal.* Such endocrine organs as can be examined by palpation or x-rays—testes, thyroid, hypophysis—are of normal size and development.

The *pathologic-anatomical* findings are: Inflammatory changes (questionable) in the *thymus* and cortical adenomata of the *suprarenal glands*. The other endocrine organs are apparently normal.

On comparison of these symptoms with the *suprarenal syndromes* mentioned before, there is a conspicuous resemblance, clinically as well as pathologic-anatomically. Both conditions show premature somatic development and histological changes in the suprarenal cortex.

I therefore found it quite obvious to interpret the congenital macrosomia as a suprarenal syndrome that falls under the *obese type* as described by Guthrie and Emery. But the rapid development of the symptoms as early as in the first month of life and their extraordinary intensity—with particular respect to the obesity—the familial occurrence of the abnormality, the persistent infantile aspect of the patients, and—last but not least—the absence of hypertrichosis and of genital abnormalities, all these features distinguish macrosomia clinically from all cases previously reported, and to such an extent that *I have thought it justified to consider the condition a distinct and separate disorder and to give it a special name.*

In order to indicate the characteristics of the abnormality as definitely as possible, I have decided on the designation: *Macrosomia adiposa congenita.*

As for the *pathogenesis* of congenital macrosomia, it would be reasonable, according to Apert's theory, to assume that the development of the symptoms is due largely to the hypersecretion of a hypothetical growth-stimulating hormone, produced in the suprarenal cortex, a cortical hyperfunction—on the anatomical basis of the cortical adenomata.

But, even though this cortical hyperfunction is an important point for the understanding of the pathogenesis of macrosomia, it is, on the other hand, a question whether it is correct to take the suprarenal symptoms, in general, and the congenital macrosomia, in particular, as manifestations of a *monoglandular dysendocrinia*. The pathologists are more and more of the opinion, that *combined* symptoms—such as in congenital macrosomia, for instance—should be interpreted as the outcome of an underlying—primary or secondary—*combined* endocrine dysfunction, a *pluriglandular dyscrasia*. Such a view is precisely in line with the principal idea in the theory of humoral correlation, namely: an intimate chemical interaction of the individual elements in the endocrine system, whose aggregate, reciprocally balanced, function is of vital importance to the maintainence and physiological development of the body. This correlation will by itself bring it about that dysfunction—qualitative or quantitative—of a single organ affects the function of the other organs so that the ensuing syndrome will be the result of functional disturbances of *several* glands.

In the case of congenital macrosomia we may assume that the congenital (idiotypical) adenomatous changes of the suprarenal cortex constitute the underlying cause of the primary cortical hyperfunction, and that this in turn produces a pluriglandular functional disturbance of the respective glands, of which disturbance macrosomia adiposa congenita is the outer manifestation.

On account of its influence on the somatic development and ossification, the *thymus* probably plays a not inconsiderable rôle among these endocrine glands. The interaction of the suprarenal cortex and thymus is well known from the pathology (status thymico-lymphaticus), and it has been demonstrated experimentally by Marine, Manley and Bauman, and Jaffe, who have shown that suprarenalectomy in young animals is followed, not only by arrest of the physiological involution of thymus, but even by regeneration of this organ.

The thymic changes (accumulation of eosinophile cells), that are found side by side with the adenomata of the suprarenal cortex in congenital macrosomia, are of a certain interest in this connection. For their presence is hardly to be regarded as a purely incidental finding.

With respect to *etiology*, congenital macrosomia *must be considered the manifestation of a hereditary property* (cf. the family occurrence of the abnormality and its phenotypical conformity in the two series of children).

This property—macrosomia—may perhaps not be hereditary as such. But here—as always in the hereditary pathology—the matter does not hinge on this or that phenotypical aspect, but on the hereditary transmission of such factors as condition the development of this property in the zygote. To understand the hereditary conditions of this property, it is therefore essential not to lay particular stress on the clinical aspect of



macrosomia, but to consider this as the reflection of an endocrine disturbance, which again is the outcome of some underlying genotypical factors.

It may be said at once that an exact account of the hereditary conditions is limited by two elements. First, the family material comprises but three generations; and second, the status of the endocrine organs we are dealing with comes within the so-called complex properties, which are conditioned, not by one single factor, but by the correlation of several factors. As a matter of course, such properties are not to be expected to comply with the simple *Mendelian* rules of dissociation, unless one of these correlating factors is constantly so dominant that the phenotypical end-result is conditioned substantially by the presence of this factor (*Siemens*).

Still, the given facts do furnish material sufficient for a hypothesis of the hereditary process in these cases.

According to the available information, there has been no instance of congenital macrosomia in the direct ascendancy within rememberable generations. Nor was this to be expected. For—like amaurotic idiocy, for instance, and congenital ichthyosis—this abnormality comes evidently within the so-called *lethal properties*, which are due to the presence of *lethal factors* (cf., 5 out of the 7 abnormal individuals died within the first year of life), and which are characterized by the very fact that carriers of the property, as a rule, die before they reach the age of reproduction. Consequently, a lethal property—in this case, macrosomia—can not have been present in any parent, grandparent, or direct ancestor of the pathological individuals; but, such a property may very well have been present in the side-branches, of which the family history is mostly defective. So, from that point of view, it is not strange that the parents and grandparents of the patients show no sign of macrosomia. It is more peculiar, on the other hand, that recessivity does apparently not occur. For one thing, the manifestation frequency makes against recessivity. In the second place, to make recessivity possible the fathers would have to be heterozygotic carriers of an allelomorphic character corresponding with the maternal one; and this is hardly probable, as the two fathers are not akin, nor either one of the same blood as his wife. *Most likely there is no transmission of a specific character from the paternal gametes in these cases.*

On the other hand, there can be no doubt whatever but that the mothers—the two sisters—share in effecting the hereditary production of the abnormality. The question is merely whether they both show any sign of characters that may conceivably have elicited the abnormal endocrine condition. And it seems to be so. As pointed out before, the sisters in question (Nos. 2 and 4) are not perfectly normal in endocrine respect, *as they both show menstrual disorders* (late menarche in one, and most irregular menses in the other); and no matter how commonplace this condition might appear, it can not be left out of consideration in this connection. For it is suggestive of a certain hereditary continuity—and

the correlation of the interrenal system and the gonads is a well-known fact. On the other hand, however, there is no indication of a regular dominance.

Apparently we are here dealing with a phenomenon that is not infrequent in human hereditary pathology, namely, the so-called *irregular dominance*—or, better, *conditional dominance*—which crops out as transformative inheritance—or *heteropheny* (*Siemens*). By this is meant that the same hereditary substrate is manifested differently in progenitor and progeny, and, further, that the particular property may be inherited through conductors, in spite of its dominant character.

The menstrual disorders of the mothers and the macrosomia of the children would then be interpreted as manifestation variations of the same basic properties and conditioned by the (non-specific) milieu, wherein the specific abnormal factors are placed through amphimixis.

The theoretical basis of the irregular dominance is this, that the effect of the specific pathological factors depends on what other—by themselves non-pathological—hereditary factors are admixed in the zygote, so that any transition may occur, from complete inhibition (inheritance through conductors) to maximal intensification of the effect of the factors in question.

The here mentioned hereditary dysendocrinia appears to imply the intensification (and anticipation) of a specific factor effect, increasing through generations and finally producing the lethal property, the macrosomia, through the admixture of such (non-pathological) *paternal* factors as let the *maternally* inherited factors crop out. So in this manifestation of heredity we are really in the border region between recessivity and dominance.

#### TREATMENT

As to the *therapy* of the congenital macrosomia, we have tried whether the ordinary organotherapeutics may have any influence on this condition. It is interesting that the very same two children, *No. 10* and *No. 14*, who were treated with such preparations, are the only ones out of 7 abnormal individuals that are still alive (see above). Whether this is due to the treatment, or whether it comes from the fact that the hospital care for several months has guarded these children against accidental injury is of course, an open question.

The experimental therapy has consisted in alternating administration of ovarian, thyroidin, and tetraglandular tablets, beside pituitrin injections. The therapeutic effect was estimated by systematic weighings and by observations on the food requirements of the children. The successive administration of the preparations was followed for several months by decrease in the rate of increasing weight (there was even a small, absolute loss of weight) and by a lowering of their craving for food, together with an apparent decrease of the diuresis.\*

\*This, too, supports the view that several glands share in effecting the development of this syndrome.

A cure of the macrosomia was not obtained, as mentioned, nor was such to be expected. But the treatment has unquestionably improved the condition of the patients, and it may probably have contributed to ward off—for a while at any rate—the sad, predestined fate of these children.

## SUMMARY

A new dysendocrine syndrome is described and discussed. On account of its clinical aspect it is called *Macrosomia adiposa congenita*. It was met with in the children of two sisters with menstrual disorders. Among 9 children, born at full term, 7 were macrosomians; and 5 of these died within the first year of life. Autopsy (1 case) showed adenomata in the suprarenal cortex and accumulation of eosinophiles in the thymus.

*Macrosomia adiposa congenita* comes probably within the *obese type* of premature development (Guthrie and Emery), depending upon a hyperfunction of the suprarenal cortex (Apert); it is in a class by itself, however, through its lack of sexual abnormalities and hirsutes. Most likely macrosomia—as well as the suprarenal syndromes on the whole—is in fact a pluriglandular syndrome.

From another point of view, macrosomia adiposa congenita may be regarded as a lethal, hereditary abnormality, whose appearance may be explained as a phenomenon of transformative heredity or heteropheny (*Siemens*).

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## TYPES OF GRAVES' DISEASE\*

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A study of over 4000 cases of Graves' disease has led me to the conviction that so-called exophthalmic goiter is arbitrarily divisible into a number of types. A prompt recognition of some of the vague forms of the disease is of manifest benefit to the patient.

In order that a diagnosis of Graves' disease be valid, the following seven evidences should be present in combination: (1) increased basal metabolism (in approximately 99.5 per cent); (2) afebrile heart hurry (in 99 per cent); (3) tremor; (4) emotionalism; (5) fatigability; (6) dermographia; (7) relative immunity to cinchonism (d) (97 per cent). Exophthalmos and goiter, while usually present, are absent in so great a percentage of cases that the term exophthalmic goiter is misleading and should become obsolete.



Fig. 1. Graves' Disease—Incipient Type.

While increased basal metabolism is absent in approximately one out of 200 patients, and tachycardia does not obtain in approximately one per cent of cases, for practical purposes these are constant enough to be considered pathognomonic of Graves' disease. The ability to take relatively large doses of quinine (1) without evidences of cinchonism is likewise a factor which, though associated with a 3 per cent error, yet is a useful asset in diagnosis.

The division of a disease into types does not imply that these present clear-cut differentiation one from the other. In all affections, and more

\*From the Bram Goiter Institute, Upland, Penn.

(1) Bram, I. Tolerance for quinine in exophthalmic goiter. *Arch. Int. Med.* 42: 53. 1928.

particularly in Graves' disease, types indicate either the customary clinical picture or a departure of the symptomatology from the usual in varying degree, frequently with the bearing of a greater burden by one bodily structure than by the remainder.



Fig 2 Graves' Disease—Chronic Type



Fig 3 Graves' Disease—Type without Goiter

#### ACUTE TYPE

The acute type of Graves' disease is rare. Its tragic course is brief and malignant, with very rapid loss in weight, extreme tachycardia, hypertension, distressing palpitation, and cardiac arrhythmia. Fibrillation, auricular and ventricular, is common. Fever may become hyperpyrexia, the temperature occasionally rising to 106 or even higher, associated with uncontrollable nausea, vomiting and diarrhea. Even hematemesis and melena may occur. Exophthalmos is marked, and trembling of the body may be so

severe as to cause vibration of the bed upon which the patient lies. The basal metabolic rate varies anywhere between plus 75 and plus 110 per cent or more. Often metabolic studies cannot be performed with accuracy because of the patient's condition. Mental derangement is common, occurring as acute delirium, dementia or mania. This form of the disease usually ends fatally from exhaustion within from a few days to a few weeks.



Fig. 4. Graves' Disease—Type without Exophthalmos.



Fig. 5. Graves' Disease—Type without Exophthalmos or Goiter.

The loss in weight may occur at the rate of one to four or five pounds a day, and cases are on record in which one-half the body weight was lost within the brief period of the patient's illness.

An acute exacerbation of the usual form of Graves' disease may approach the primary acute type in severity and is the usual cause of post-operative death. During the course of thyroidectomy or immediately after, commonly as the patient comes out of the anesthetic, there occur great excitation, marked delirium, exaggerated tremor, extreme anxiety, drenching sweats, and, at times, hallucinations and mania. The pulse mounts to

180, 190 or even 200 per minute, soon becoming feeble and impalpable; there is high fever, vomiting, and incontinence of urine and feces, usually terminating in fatal collapse within a few hours or a day or two. Post-operative crises are not quite so frequently encountered since the advent of the preoperative and postoperative use of iodine.



Fig 6. Graves' Disease—Type with Unequal Exophthalmos.



Fig. 7. Graves' Disease—Thyroid Type.

- A. Patient who had been thyroidectomized about a year before in a representative clinic. The thyroid had regenerated to an extent that knew no bounds and caused pressure symptoms.
- B. Case in which iodine had caused such tremendous enlargement of the thyroid as to occasion pressure symptoms.

Thought not quite as severe as the above forms of acute Graves' disease, the crisis commonly observed in the average untreated or unsuccessfully treated case yields a clinical picture replete with anxious moments. The basal metabolic and heart rate are decidedly increased, loss in weight is accentuated, mental symptoms become pronounced occasionally to the

extent of insanity, and gastrointestinal symptoms, especially nausea, vomiting, and diarrhea may become so unmanageable as to endanger life. This may continue for a period of from a few weeks to a few months, and if the patient possesses sufficient recuperative power there occurs a gradual recession of the severity of the symptoms and once more the syndrome is that of the average case.



Fig. 8. Graves' Disease--Type with Adenoma.

- A. Graves' Disease of protracted duration in which there occur adenomatous infiltration within the thyroid.
- B. Graves' disease superimposed as an independent entity upon a previously existing simple thyroid adenoma.

Occurring in the average form of the disease even while the patient is tangibly improving, is the acute onset of an exaggerated symptomatology resulting from the superimposition of a recent psychic trauma or shock. Such events as automobile accidents, the sudden death of a relative, a narrow escape from a conflagration, and in one instance resulting fatally, sudden separation from her husband, were exciting causes in our series. A formerly mild case becomes severe, a sane patient insane, an organically good heart may undergo serious dilatation and fibrillate badly, and a patient in whom the prognosis appeared excellent may become moribund.

#### INCIPIENT FORME FRUSTE TYPE

The early or incipient or *forme fruste* type of the disease may be somewhat difficult to recognize. The eyes may present a stare with but little tangible bulging; the thyroid gland may not be tangibly goitrous; the heart rate may be normal or increased to 90 or 100 per minute; the tremor may be unrecognizable to the inexperienced eye. Changes in behavior, nervousness, restlessness and insomnia, are in the larval stage. There may be no loss in weight; because of the excessive appetite there may indeed be an increase at this time. The basal metabolic rate may be either normal or not in excess of plus 15 or plus 20 per cent, and the patient may feel and appear in good health. On questioning, he may admit the pres-



ence of some palpitation on slight exertion, some dyspnea, nervousness and undue fatigue, but there may also be a sense of unusual exhilaration. While most cases of incipient Graves' disease develop the affection in typical form, a small percentage remain mild or early cases for an indefinite period or throughout life. Many cases of so-called puberty hyperplasia belong in this group.

#### AVERAGE TYPE.

The average typical case of Graves' disease requires little comment, since exophthalmos, swollen thyroid, tremor and tachycardia, render diagnosis an easy task. The condition is usually the development of the early or incipient type, although the period of transition may not be great enough to be recognized during the early stage. In other words, the average case of the disease occasionally develops more or less sharply, requiring a period of a few weeks for its full development. The well-known other features such as a pulse rate exceeding 100 per minute, a basal metabolic rate exceeding plus 20 per cent, the dermatographia, sweating, loss in weight, muscular weakness, emotionalism, insomnia, and frequently diarrhea, are too well known to be discussed in detail.



Fig. 9. Graves' Disease—Cardiac Type.

- A. Severe Graves' disease associated with marked cardiac hypertrophy, hypertension and impending decompensation.
- B. Same condition, including marked auricular fibrillation.

#### CHRONIC TYPE.

Chronic typical Graves' disease is a term applicable to a form of the disease easily recognized, but rarely reaching a crisis. If crisis occurs it is not perilous. The incipient form of the disease has merged into the more characteristic and easily recognizable type, but the patient does not feel sick enough to abstain from daily duties and carries on about as before. An occasional day or a week may be spent in resting, but, generally speaking, there is no period of subjective invalidism. The skin is unduly moist, but the tremor is moderate and does not interfere with work. The heart

rate may not exceed 80 to 100 per minute, and may not be disturbing unless on unusual provocation. The thyroid gland may be moderately swollen and typically hyperplastic. The eyes, too, may present all the features of the average case. The weight may or may not be markedly reduced; and while on occasion there is marked emaciation, not infrequently a formerly obese individual may still appear obese. During remissions the basal metabolic rate may be quite within normal limits, and occasionally may even present a minus reading. During the more active stage corresponding to pseudo-crisis, it may not exceed plus 15 to 20 per cent. This form of Graves' disease may continue on without sharp manifestations for ten or more years, when spontaneous recovery may occur, with or without evidences of myxedema. Occasionally, too, an added psychic trauma may change this type to one of greater severity.



Fig. 10. Graves' Disease—Cardiac Type.

- A. Very severe Graves' disease with badly degenerated heart, decompensation with anasarca.
- B. A similar case in one who had undergone two thyroidectomies. Duration of Graves' disease over 14 years.
- C. Beginning cardiac decompensation in a case of Graves' disease of approximately 10 years' duration.

Remark: In each of these cases auricular and ventricular fibrillation was very marked.

As a result of thyroidectomy but more often of x-ray treatment, a formerly average type of Graves' disease may become milder and chronic, without crises and often with some evidences of myxedema. Among the patients of our series is that of a man whose Graves' syndrome was of 20 years' duration, the x-ray treatments having been administered 15 years before.

Again, a formerly severe or average case of Graves' disease may undergo spontaneous remission and remain as a milder, chronic case for years or throughout life, the end resulting from events incident to an acute infection, chronic myocarditis, insanity, or a crisis following a superimposed psychic trauma.

## TYPE WITHOUT GOITER.

No thyroid enlargement occurred in approximately 19 per cent of this series. In other respects the syndrome did not differ from the typical. Here we must bear in mind that thyroid swelling is usually the last event in the syndrome. Occasionally we note goiterless patients whose symptoms are more severe than those of the average. Since a normally appearing thyroid area does not preclude the possibility of an intrathoracically located thyroid, the examiner must be capable of palpating the lower border of the thyroid, and when this is impossible an x-ray examination must be made. More rarely, a patient with a normally appearing thyroid may present aberrant thyroid hyperplasia situated in relation with the pharynx, tongue, trachea, ovaries, or elsewhere.



Fig. 11. Graves' Disease—Pituitary Type.

- A. Case of postoperative Graves' disease, myxedema, and acromegaly, in a man who had been thyroidectomized in a representative clinic.
- B. A thyroidectomized sufferer from acromegaly.
- C. A case of atypical Graves' disease and acromegaly in a woman who had not been operated upon.

## TYPE WITHOUT EXOPHTHALMOS.

Exophthalmos was absent in 12 per cent of cases in this series. We must recall that in patients without exophthalmos it may occur in the advanced stage of the disease. Graves' disease without exophthalmos misleads diagnosis, especially when it is a question of differentiation from toxic adenoma. While a few observers have asserted their belief that exophthalmic goiter and toxic adenoma are virtually synonymous, there are so many points of difference in the inherent makeup of the individual, the history of the case, and the syndrome itself as to render their conclusion untenable. The uncommon instance in which Graves' syndrome is superimposed upon toxic adenoma with the superaddition of exophthalmos, merely indicates the existence of two distinct unrelated diseases. The points of similarity and of difference between toxic adenoma and exophthalmic goiter are as little and as great as the similarity and difference between chickenpox and smallpox.

## TYPE WITHOUT EXOPHTHALMOS AND GOITER.

Graves' disease without exophthalmos and goiter is often most confusing, for it is here that such diagnoses as effort syndrome, paroxysmal tachycardia, hysteria, neurasthenia, early tuberculosis, and various other conditions are made. Graves' disease without exophthalmos and goiter usually presents a syndrome more amenable to treatment than the typical form of the disease.



Fig. 12. Graves' Disease—Adrenal Type.

## TYPE WITH UNEQUAL EXOPHTHALMOS.

A patient may present unilateral slight exophthalmos, and by the time this becomes quite marked, the other eye may begin to protrude slightly, and throughout the course of the disease one eye may bulge more than the other. Again, during the process of recovery one eye may recede to normal while the other bulges for a time after the patient is well. Occasionally a patient may present unilateral exophthalmos throughout the entire course of the disease. There is no relationship between unequal or unilateral exophthalmos and the degree of swelling of the thyroid on one side or the other, nor is there any relationship between unequal or unilateral exophthalmos and the severity, course or prognosis of the disease.

## VAGOTONIC TYPE.

The vagotonic or parasympathetic type of Graves' disease is characterized by a relatively slight increase in heart rate and little or no subjective heart symptoms. Exophthalmos is slight, the pupils contracted, there is a wide palpebral fissure with a marked von Graefe sign, and the eyes are excessively moist. Excessive sweating occurs; there is intractable diarrhea and considerable bladder irritability. There is a tendency toward hyperchlorhydria and respiratory arrhythmia. The hair does not fall out

as in the case of sympatheticotonia, and there is no tangible reduction in carbohydrate tolerance.

#### SYMPATHETICOTONIC TYPE.

The sympatheticotonic type of Graves' disease presents marked persistent tachycardia and subjective heart symptoms. Exophthalmos is severe, pupils are dilated, the Moebius sign is present, and epinephrin mydriasis is elicited. The eyes and skin are comparatively dry. There are no diarrhea, bladder irritability, hyperchlorhydria, nor respiratory arrhythmia. The temperature is frequently elevated to within one or two degrees above normal. There is a tendency to falling out of hair and a reduction in carbohydrate tolerance.



Fig 13 Graves' Disease—Obese Type

These patients illustrate Graves' disease in individuals who despite a high metabolism present a weight considerably above 160 pounds.

Let it not be supposed that sympatheticotonia or vagotonia occur as distinct entities in the clinical picture. Any attempt to check up the findings in a given patient will yield many apparent inconsistencies, so that a classification of exophthalmic goiter on this basis can be made in a relative sense only. In the average case, sympatheticotonia seems to dominate over one group of complaints and vagotonia over another, without either division of the autonomic nervous system gaining complete control. It is only when one or the other part of the involuntary nervous system holds excessive sway over the clinical picture that we might designate the type of the disease accordingly.

#### THYROIDAL TYPE.

To say that there is a thyroidal type of Graves' disease may be regarded as an obvious statement. When, however, we take into account the view that the thyroid is not the cause of the syndrome and when we recall that in many cases the gland does not become swollen, the need for a de-

scription of a "thyroid type" of the disease is apparent. By the thyroidal type I refer to that form of the disease in which the thyroid participates to an unusual degree in the symptomatology and, as it were, runs away with the patient. This is comparable to the common clinical phenomena in which a tonsillar infection, producing secondary rheumatic endocarditis, the latter assumes the ascendancy. The cause (largely unknown) of Graves' disease having produced thyroid hyperactivity, the latter dominates the symptomatology. The thyroid is tremendously enlarged, often to the extent of producing dyspnea, dysphagia and dysphonia. Sleep occurs in fits and starts and in a given position to ease the pressure upon the neck. In this type thyroidectomy appears the only rational therapeutic procedure. Approximately 2 per cent of cases may be considered as belonging to this type.



Fig. 14. Graves' Disease—Insane Type.

- A. This patient had undergone a double ligation and developed manic depressive insanity shortly thereafter.
- B. A patient who had undergone subtotal thyroidectomy and who developed a major psychosis within a few months thereafter.

#### TYPE WITH ADENOMA.

A sufferer from adenoma (either simple or toxic), may develop Graves' disease as an incident. The development of exophthalmos, excitability, and all the other characteristics of Graves' disease in a patient who has had an adenoma of the thyroid for some years is no reason for concluding that we have before us a case of "toxic adenoma with exophthalmos." There is no more reason to believe that Graves' disease cannot occur in a sufferer from thyroid adenoma than that the rash of measles cannot occur in a sufferer from chronic eczema.

Again, an oldstanding Graves' disease with thyroid hyperplasia may rarely undergo adenomatous, cystic, or even calcareous changes. In such an event the history of the case reveals that the various nervous manifestations of Graves' disease preceded thyroid enlargement, and that the goiter became less throbbing and less symmetrical in the course of time.

## PANCREATIC TYPE.

While in nearly all cases of Graves' disease there exist a degree of carbohydrate intolerance, in approximately 3 per cent the blood-sugar approaches the height observed in diabetes and in approximately one per cent diabetes actually exists as a complication. In these cases we face a problem resembling the combination of tuberculosis with diabetes mellitus, namely the fact that the one disease requires forced feeding, the other considerable starvation.

Acidosis during the course of Graves' disease is a problem requiring determination whether acidosis is due primarily to a crisis in the syndrome or to a complicating diabetes, or both.



Fig. 15. Graves' Disease—Postoperative Type. These two illustrations represent individuals who, despite expert thyroidectomy, are nevertheless suffering with Graves' disease in severe form.

## CARDIAC TYPE.

Cases in which cardiac manifestations dominate the symptomatology may be regarded as cardiac types. The heart beats violently against the chest wall, resulting in marked discomfort and even pain. In one woman of 45 the symptoms were practically identical with those of angina pectoris. The heart rate may be out of proportion with the basal metabolic rate and the other symptoms. The blood pressure is either normal or presents a varying degree of hypertension. When decompensation is impending the blood pressure is restored to the normal figure or below. During treatment the basal metabolic rate and all other symptoms of the disease may be fairly well under control, yet the heart may still be racing for a variable time.

## THYMUS TYPE.

The thymus type of Graves' disease is often seen. Graves' disease is commonly associated with enlargement of the thymus. If this organ is unusually large, tachycardia and other constituents of the syndrome are

accentuated. Male patients in whom dyspnea is out of proportion to the remaining symptomatology, whose skin is more or less of the "peaches and cream" hue, whose lymphatic glands are somewhat more prominent than usual, and whose general demeanor partakes somewhat of feminine trend, can be assumed to present the thymic form of exophthalmic goiter. While x-ray examinations are of assistance in diagnosis, they are not always convincing nor conclusive.



Fig. 16. Graves' Disease—Postoperative Type.

These three patients present a combination of marked myxedema and residue of Graves' disease following surgical attention at representative clinics.

#### PITUITARY TYPE.

The patient presenting suggestive evidences of acromegaly may be regarded as a sufferer from the pituitary type of Graves' disease. A leonine expression and some thickening of the fingers and toes characterize this type. Evidences of somatic pituitary involvement may be observed in unoperated as well as operated patients. In those of adolescent age augmentation in height, even to the point bordering on gigantism, is occasionally observed.

#### ADRENAL TYPE.

White dermographia, hypotension in which the systolic blood pressure may not exceed 90 or 100 mm., an overpowering fatigability, and large patches of pigmentation covering the face, limbs, body, and even the mucous membranes, characterize the adrenal type of Graves' disease. Rarely, if ever, do these patients develop Addison's disease.

#### GONADAL TYPE.

In women the gonadal type of Graves' disease expresses itself in the presence of uterine or ovarian neoplastic conditions, sterility and marked menstrual abnormalities. In the male, sexual neurasthenia, priapism, and inferiority complexes of a sexual nature in which the mentality is more or



less directed toward the sexual self characterize this type. Sexual organs and functions are overemphasized. In most such instances the etiology of the disease is traceable to the sexual structures and life of the individual.

#### OBESSE TYPE.

Graves' disease with obesity instead of emaciation, even in the presence of a high metabolic rate, is not unusual. The present weight may represent the natural tendency toward overweight, but not to the former extent. Thus a patient may present a weight of 160 or 180 pounds which may represent a loss of 30 or more pounds from the former obesity. Also we observe cases in which the weight before the onset of the disease was, let us say, 140 pounds, and now is increased to 150 or more. The appetite being keen in Graves' disease and the gastrointestinal tract in perfect condition, a quantity of food was taken which corresponded to more than the needs of the individual, even with the excessive catabolism, and the weight became augmented. Usually the course of the disease eventually leads to tangible loss in weight.



Fig 17. Graves' Disease with Hypertension.

- A. Case of severe type of Graves' disease in a woman of 67 with systolic blood pressure of over 200 mm.
- B. A similar case in a younger woman with a systolic blood pressure of approximately 190 mm

#### INSANE TYPE.

There are three forms of Graves' disease with insanity: (1) Patients who possess an inherited trait of insanity, in whom from the very outset the symptoms of the disease may be predominantly psychic. The first evidence observed may be a departure from customary behavior. The patient acts queerly and converses irrelevantly. As the disease progresses, this becomes accentuated, and in course of time a clear-cut psychosis is evident. (2) Patients who, without any known hereditary tendency, suddenly develop insanity during the course of the disease. Occasionally this may be engendered by a crisis with or without a preceding psychic trauma. The

individual becomes unmanageable, and the psychosis predominates and becomes the major problem. (3) Insanity as a result of the added shock of an operation. In our series of 18 cases of insanity complicating Graves' disease, 10 occurred in previously thyroidectomized patients. The psychosis is usually of the manic-depressive type, associated with a strong tendency to self-destruction based upon an inferiority complex and self-accusatory delusions, and accompanied by visual and auditory hallucinations. Persecutory delusions may also occur.

#### POSTOPERATIVE TYPE.

The outstanding features of postoperative Graves' disease as compared to the average primary form are: (1) The course is usually more protracted, response to therapeutics being rather tardy. This applies more especially to the circulatory and nervous system and the exophthalmos.



Fig. 18. Graves' Disease—Juvenile Type.

- A. Typical Graves' disease of severe type in child of a little over 11 years old.
- B. Severe Graves' disease in a youngster of 9.

(2) Thyroid gland regeneration is apt to resist all efforts at control for a considerable time. Indeed, the regenerative process is occasionally so mushroom-like as to lead to the formation of a goiter greater in size than was the original mass. (3) The contrary may likewise be true—the operated thyroid gland presenting such reduced function as to occasion myxedema despite the fact that the original symptoms of Graves' syndrome are largely prevalent. (4) The major psychoses, more particularly manic-depressive insanity, have a greater predilection for thyroidectomized patients than those who had not been operated upon.

#### NORMAL PULSE TYPE.

In approximately one per cent of cases, the syndrome, though typical in all other respects (including a basal metabolic rate of over plus 15 per

cent) yet presents a normal pulse rate. This is obviously a vagotonic manifestation, though the other symptoms may not be predominantly vagotonic.

#### LOW METABOLIC TYPE.

The low metabolic type of the disease (in unoperated cases) occurs in approximately 0.5 per cent of cases. Despite all evidences of typical Graves' disease, the basal metabolic rate is entirely within normal limits.



Fig. 19. Graves' Disease—Senile Type.

A. Patient 64 years old.

B. Case of severe type in a woman of 74.

#### HYPERTENSION TYPE.

While hypotension characterizes the average case of Graves' disease, occasionally the reverse is true in which the systolic blood pressure reaches 175 or even 200 mm. These cases may be divided into three classes: (a) those in which hypertension is secondary to a preceding hypotension, the increased blood pressure being the result of circulatory hypertrophy; (b) those with arterial sclerosis in which Graves' disease occurred rather late in life; and (c) patients in whom Graves' disease is complicated with an independent malignant hypertension.

#### JUVENILE TYPE.

In this series of 4000 cases, 43 were under the age of 12. A few occurred in children of three or four years old. While the circulatory and nervous systems bear the brunt of the syndrome, exophthalmos and thyroid swelling are usually moderate. The heart rate is frequently so rapid as to be entirely out of proportion with the remaining symptoms. Nausea, vomiting and diarrhea are not as frequently observed as in adults. Graves' disease in the growing child approaching puberty is frequently associated with marked augmentation in height, implying unusually active pituitary participation.

## SENILE TYPE.

In our series approximately 6 per cent are beyond the age of 60. We might term this form of Graves' disease as the senile type, and their characteristics are as follows: Moderate or no thyroid enlargement, moderate exophthalmos, marked tremor, a strong tendency to hypertension, and in the presence of appropriate cooperation, satisfactory prompt response to appropriate medical attention.

## SUMMARY.

In the foregoing remarks, 26 varieties of Graves' disease are briefly described. These types indicate not clear-cut species of the disease, but an accentuation or prominence of a symptom or symptoms within a clinical picture presenting many features commonly observed in all cases.

The division of Graves' disease into types is therefore largely useful arbitrary device to stimulate a deeper study of the subject and an earlier recognition of the disease in the event of marked departure of the symptomatology from the average case.

A division of Graves' disease into types will also hasten the day when it will be generally realized that Graves' syndrome can mimic more affections than any other disease in the domain of medicine, and will gain approbation to the view that since Graves' disease is neither goiter nor appears to be purely a disease of the thyroid, the synonym, exophthalmic goiter, should become obsolete as misleading and a deterrent to progress.

# FROEHLICH'S SYNDROME AND ROENTGEN-RAY: SOME REFLECTIONS ON A CASE OF DYSTROPHIA ADIPOSE- GENITALIS

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## CLINICAL HISTORY OF THE PATIENT

S. S. is 17 years old; 1.68 M. tall and weights 87 kgm. His face as well as the rest of his body shows a marked adiposity which forms folds on the cheeks, on a level with the lower eye-lids, which makes us think of myxedema and gives the patient's face the appearance of having a permanent smile.

*Pathological antecedents.* The patient has very seldom been ill, but about 3 years ago he had small-pox following which he began to get fat till he reached his present state. It is important to note that S. S. had been growing rapidly until he was completely cured.

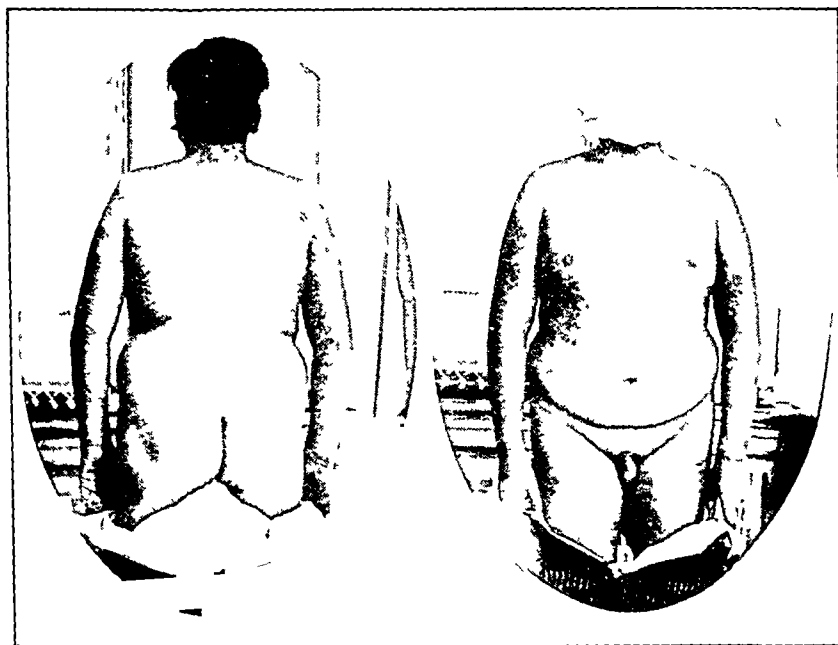


Fig. 1—View of patient's back (November, 1926 )  
Fig. 2—Front view of the same patient (November, 1926 )

*Family history.* The only points worth noting are that the patient's father has nervous tics, a choreiform gait and suffers from diabetes.

*Clinical examination.* Naked, what most calls our attention is the marked gynandromorphism (quite feminine pectoral and abdominal outlines, great accumulations of adipose tissue on his pectorals, hips and mons veneris.) See Figs. 1 and 2.

The skin of the mons veneris forms a fold which extends on both sides of the lower abdominal region. The genital organs are rudimentary, the penis is very small and undeveloped and the right testicle almost imperceptible. (Fig. 3). The skin of this region is destitute of hair as is the rest of the body (chest and armpits). He has no sexual instinct. He has never had an erection, and has a slight genu-valgum. The Roentgenogram of the hands shows persistent epiphysial lines. (Fig. 4.) The

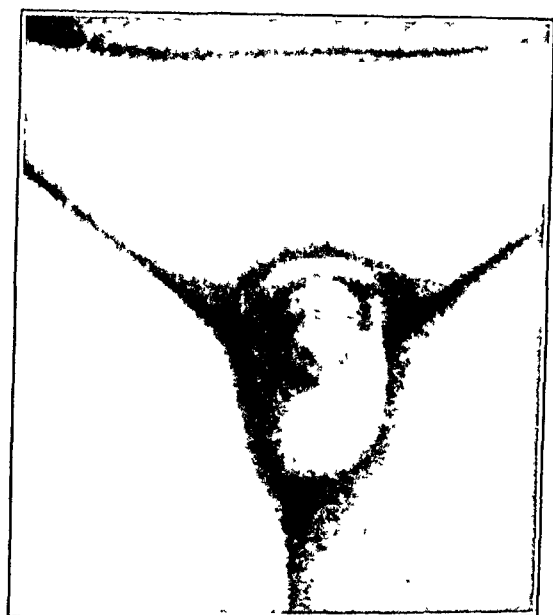


Fig. 3—Aspect of the genital organs. (November, 1926.)

Roentgenogram shows no abnormality of the sella turcica. (Fig. 5.) The patient's inclinations are towards children's games and to study. He has a good memory and great capacity for the cultivation of the sciences and above all for arithmetic. Educated in religious institutions, he seems to feel a certain propensity towards mysticism.

He has a good appetite, and does not suffer from constipation or diarrhoea.

He has no respiratory or circulatory anomalies.

His nervous system is well developed and does not show any disorder at all. He has great resistance against fatigue.

The urine does not show anything unusual in its composition and the daily quantity varies between 1500 and 2000 cc.

*Pharmacodynamic tests.* Goetsch's test gives a negative result. The Claude-Porak hypophysine tests (post. lobe) also give negative results: the arterial pressure (Max.=15 and Min.=8) increases one degree, but his pulse does not change. The thyroidine test of Parisot-Richard does not alter either the pulse or the pressure.

*Basal Metabolism*

(24th November, 1926)

*Result:* 1.557 Cal. per minute. 2242 Cal. in 24 hours.

*Standards:* Krogh, 1.387 Cal. per minute.

Boothby, 1990 Cal. in 24 hours.

*Deviation:* +12% (Krogh).

+13% (Boothby).

(Determinations made by Dr. Bellido. Cátedra de Terapéutica de la Fac. de Med. of Barcelona.)

*Diagnosis.* In effect, this is made directly and by exclusion. In both aspects we can be sure that the case of S. S. is one of a syndrome described by Fröhlich and termed by Bartels dystrophia adiposo-genitalis. That the disorder from which he is suffering may have been occasioned by malfunction of the thyroid gland is excluded by the pharmacodynamic tests and the basal metabolism. Moreover, the patient states that he has been

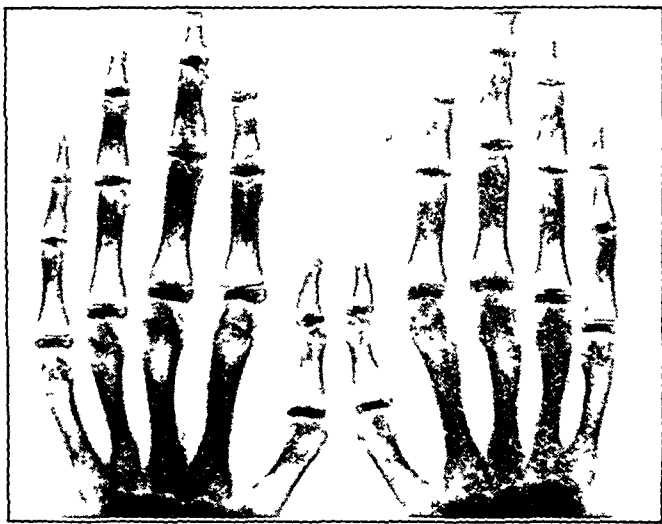


Fig 4—Roentgenogram, patient's hands (November, 1926)

taking thyroidine for 2 years, in accordance with the prescription given by the Doctor who attended him, because his disease had been diagnosed as hypofunction of thyroid gland. Before the patient visited us for the first time, this treatment had been intensified without any useful result being obtained.

That the case is one of essential primary eunuchismus is excluded by the gynandromorphism and the proportional length of the extremities.

The origin of the hypophysial disorder which has to be considered as natural in the case in question is the small-pox, which the patient had 3 years before, because the first signs of the present syndrome appeared during his convalescence from this illness.

*Where does the lesion lie?* Of late years the physiology of the hypophysis has been, it may be excessively, simplified in the sense of considering it as a triple gland (anterior lobe, posterior lobe and pars intermedia). The posterior lobe has been taken to be a simple organ regulating fat metabolism or at least as regulating fat distribution in the body. From this it has been deduced that the dystrophia adiposo-genitalis must necessarily be the result of hypofunction of the posterior hypophyseal lobe. On the other hand to the anterior lobe has been ascribed control of growth and of the development of bone and the genital organs. The pars intermedia is supposed to have the same function as the posterior lobe although more intensely.

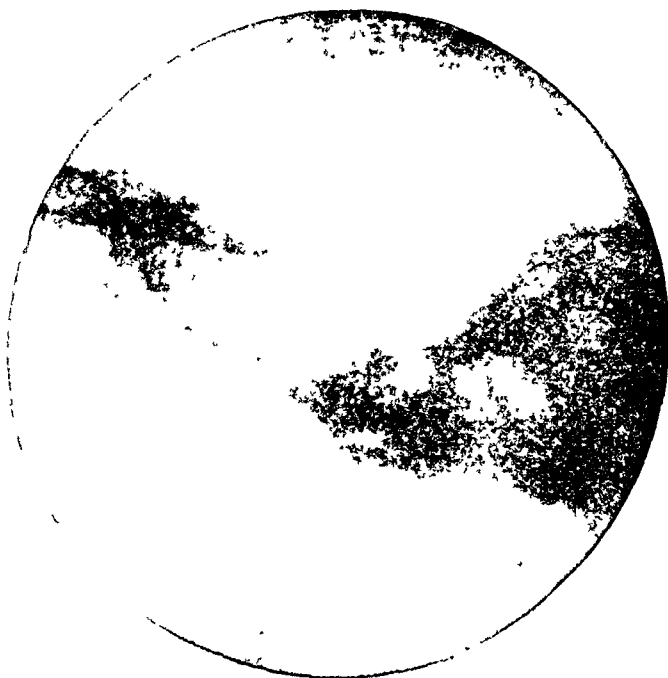


Fig. 5—Cranial roentgenogram of S. S.

If we accept this scheme as a whole we are obliged to admit in consequence that in our patient the whole of the gland has been attacked and has become hypofunctional.

*Treatment.* Admitting the logic of the hypothesis of the complete hypofunction, we tried to stimulate the whole function of the hypophyseal gland, choosing for preference the x-ray.

#### SUMMARY OF THE ROENTGEN-RAY TREATMENT

From 11th December, 1926, to 27 August, 1927, he was given 13 applications of  $\frac{1}{4}$  of an Erythema dose upon the skin of different parts of the cranium (small in size in order to avoid depilation). In each application the F. S. D. was 35 cm. with port  $6 \times 8$ ; K. V. S. 200 and 4 mA; filter 0.5 mm. Cu and 2 mm. Al.

The total radiation of the skin was 3.25 E. D., the total dosage received by the hypophysis was 1.12 E. D.



## DATA OF THE SITTINGS AND PARTIAL DOSES

11th December, 1926—	Left temporal,	(10% E. D.)
18th       "       "	"       "	"       "
29th       "       "	Right   "	"       "
8th January, 1927—	"       "	"       "
14th       "       "	Anterior frontal	( 7%   "   )
24th       "       "	Middle occipital	"       "
28th       "       "	"       "	"       "
26th March,       "	"       frontal	"       "
2nd April,       "	Anterior   "	"       "
9th       "       "	Upper parietal	(10%   "   )
25th June,       "	Anterior frontal	"       "
9th July,       "	Posterior occipital	"       "
27th August,     "	Right frontal	( 7%   "   )



Fig. 6—Aspect of genital organs in August, 1927.

*Results.* The first results of the treatment were demonstrated after considerable delay by a marked decrease of the fat in the pectorals and in the upper zone of the hips, an increase of the diuresis (quantities above 2 litres without ever reaching 3) and the appearance of the first hairs on the genital organs. Suddenly, after 6 months' treatment (10 sittings), erections began to take place and the sexual instinct awakened. At this time the sexual organs were fairly well covered with hair, the aspect of the penis almost normal and the left testicle quite normal, while the right one had undergone marked development. (Fig. 6.) The fold of adipose tissue above the mons veneris had disappeared and the features had become much more plainly marked.

At this point of the treatment, the basal metabolism was once more determined. The following results were obtained:

*Basal Metabolism*

(24th July, 1927)

*Result:* 1.522 Cal. per minute; 2185 in 24 hours.*Standards:* Krogh, 1.404 Cal. per minute.

Knipping, 2107 Cal. in 24 hours.

*Deviation:*  $+.08\%$ 

(Dr. Bellido. Cátedra de Terapéutica de la Fac. de Med. of Barcelona.)

In spite of his appearing to get thinner, the patient has gained 1 kgm. compared with his weight on beginning the treatment. It is also worth noting that during all this time he grew 2 cm. in height. The date of the last sitting was 27th August, 1927.

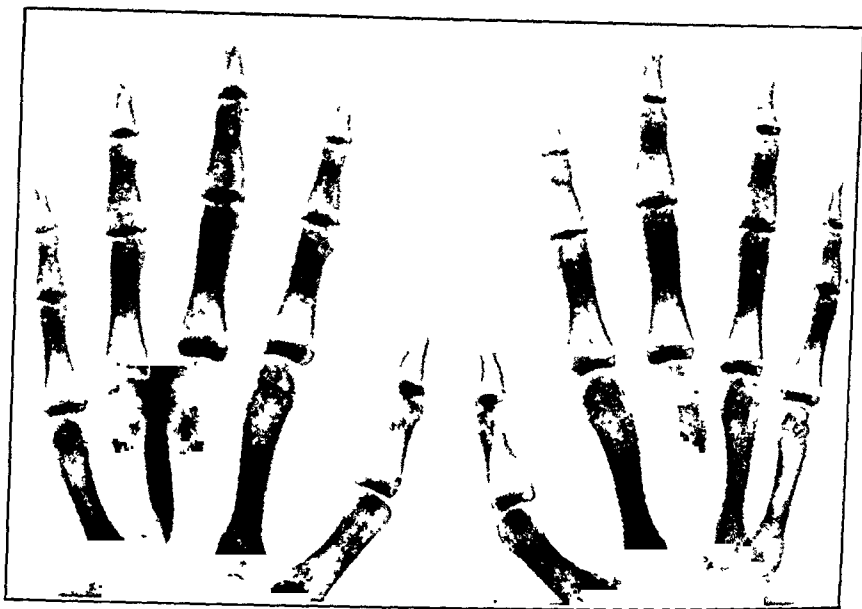


Fig. 7—Roentgenogram of patient's hands in August, 1927. The epiphyseal lines still persist and it is noted that the hand has grown 1 cm. in length.

The final examination was made on the last of October and from it we deduce that S. S. is already a normal individual carrying out in a proper manner all the physiological functions, feeling all the restlessness of the normal male, and offering in the clinical examination an harmonious organic configuration. A roentgenogram shows, however, that the epiphyseal lines have not yet become ossified. (Fig. 5.) This particularity has sufficient importance for us to leave it to be dealt with in another article.

The boy's father, given the results obtained, states privately that he is afraid that we may have given him too much treatment, because his fondness for study and his mysticism have disappeared and their places have been taken by a great liking for the cinema and dancing.

It is very probable that more than one case of dystrophia adiposo-genitalis, considered as a symptomatic manifestation of the classic eunuchis-

mus, has been a simple state of hypofunction or disfunction of the hypophyseal gland, or it may be a veritable Fröhlich's syndrome due to functional disorders of the hypophysis without neoplasm.

Those who may feel themselves inclined to believe that the case dealt with in this article may be one of those belonging to the category of primary eunuchismus will be able to obtain from the result of the x-ray treatment of the hypophysis ample scope for meditation.

# DIABETIC COMA WITH MARKED HYPERGLYCEMIA AND RECOVERY: REPORT OF A CASE

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AND

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Relatively few cases of very marked hyperglycemia in diabetic coma, with recovery, have been published; consequently it seems worthwhile to report a case that we have had opportunity to study.

The patient, a man aged 50 years, entered the University of California Hospital on July 31, 1928, in coma. He had had symptoms of diabetes for the previous 18 months, but for the past 6 months a feeling of lassitude and weakness had been steadily increasing. His weight had decreased from 220 pounds to 195 pounds. All his teeth had been extracted just three weeks before entry with the hope of improving not only his general condition but also a neuralgic pain that had recently developed in his right arm. Instead of the anticipated improvement, however, his symptoms increased to such an extent that his vision became blurred and severe restlessness accompanied by mental depression developed. Notwithstanding these danger signals no medical advice was sought, and he finally sank into profound diabetic coma.

He entered the hospital at 1 P.M. on July 31, 1928. His face was deeply flushed, skin dry, lips a cherry red, and his breath smelled heavily of acetone. He was irrational and extremely restless. His temperature was 37° C (rectal); pulse 104 and markedly irregular due to multiple extra systoles. The respiratory rate was 32; there was but slight evidence of air hunger. Blood pressure was 130/80. Urine examination showed complete reduction of Benedict's Solution and acetone++++. *Blood sugar determination revealed the unusual hyperglycemia of 1090 mgm. per 100 cc. of blood.* The plasma was creamy white, and the blood cholesterol content was 705 mgm. per 100 cc. Unfortunately the test for plasma CO<sub>2</sub> was spoiled before the material reached the laboratory.

The immediate treatment, besides the giving of insulin, consisted of gastric lavage with warm water, heat to the extremities, and hypodermoclysis of 500 cc. of normal salt solution. Very soon the patient was able to take fluids by mouth, and 2500 cc. of water was given in the first 12 hours.

The urine was tested every half hour and insulin administered, the dosage varying with the degree of reduction of Benedict's solution but not exceeding 20 units per dose. From 15 to 20 units was given every

half hour so that after seven hours the patient had received 210 units. At this time the blood sugar was 601 mgm. and the blood cholesterol 670 mgm. per 100 cc. His general condition appeared to be unchanged. In the next  $3\frac{1}{2}$  hours, he received an additional 160 units of insulin. Thereafter for the ensuing eight hours, because the urine (tested hourly) was either entirely sugar free or nearly so, no insulin was administered. Fluids were, however, continued. At the end of this time the urine showed only a trace of sugar.

At 8 A.M., August 1, the blood sugar was 516 mgm. and the blood cholesterol 400 mgm. per 100 cc. He was now wide awake and quite alert mentally. In the first 24 hours he received 405 units of insulin and 5950 cc. of fluids consisting of 600 cc. of orange juice, 600 cc. of gingerale and 4750 cc. of water.

For the next 24 hours the urine was tested for sugar every hour from 8 A.M. until 10:30 P.M. and insulin was again administered in dosages depending upon the amount of reduction of Benedict's solution. In all, 260 units of insulin was given during this period. The patient's food consisted of 550 cc. of orange juice and 400 cc. gingerale, and the total fluid intake was 4075 cc.

On the morning of the third day the fasting blood sugar was 282 mgm. per 100 cc., and the blood cholesterol 362 mgm. A program, similar in all respects to that of the preceeding day, was maintained except that only 165 units of insulin was given. The patient received 600 cc. of orange juice and 300 cc. of gingerale, as part of a fluid intake of 3500 cc.

The fasting blood sugar on the fourth day was 154 mgm. per 100 cc. but the blood cholesterol remained somewhat high, at 345 mgm. The insulin given on this day amounted to 135 units. In addition to the fluids two soft boiled eggs were allowed.

On the fifth day he received the same amount of food—and only 75 units insulin.

A regimen was then established consisting of the following diet: CHO—100 gm., P.—40 gm., F.—10 gm. (calories—650). Insulin was given in four doses, 30 units before breakfast, 30 units before lunch, 30 units before supper and 10 units at midnight. In three days it was possible to lower the insulin by 5 units per dose. From that time on the diet was gradually increased and the insulin decreased until within two weeks after entry into the hospital, the patient was on a diet of CHO—100 gm., P.—75 gm., F.—75 gm. (calories, 1375) with 20 units of insulin before breakfast, 15 units before dinner, and 20 units before supper. His fasting blood sugar was 170 mgm. per 100 cc. and cholesterol 207.5 mgm. He remained in the hospital an additional four days, 18 days in all. On discharge from the hospital he felt well and strong and his urine was entirely sugar free. It will be noted that no alkalis were administered. It is felt that they are not only unnecessary but may at times actually produce harmful results.

A fairly extensive review of the literature reveals but two reports of individuals who recovered from diabetic coma when the initial blood sugar determinations were higher than that found in this case. Curtis (1) reported the finding of a blood sugar of 1680 mgm. per 100 cc. of blood and Foster (2) has had a patient whose blood sugar was 1260 mgm. The extreme hyperglycemia of 1740 mgm. per 100 cc. of blood reported by Argy (3) is the highest yet recorded, but his patient died. Other cases of marked increase in the blood sugar content have been reported by Pitfield (4)—1700 mgm. per 100 cc., by Joslin (5)—1370 mgm. and by Paddock (6)—1040 mgm. Their patients, however, failed to survive.

## SUMMARY OF TREATMENT IN CASE RECORDED

	Blood Sugar	Insulin	Fluid
1st 24 hours.....	1090 mgm. per 100 cc.	405 units	5950 cc.
2nd 24 hours.....	516 mgm. per 100 cc.	260 units	4075 cc.
3rd 24 hours.....	282 mgm. per 100 cc.	165 units	3500 cc.
4th 24 hours.....	151 mgm. per 100 cc.	135 units	ad. lib.
5th 24 hours.....		75 units	ad. lib.

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# ELECTROCARDIOGRAPHIC SIGNS ASSOCIATED WITH LOW BASAL METABOLISM

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In recent years the endocrine glands and conditions due to their malfunction have been subjected to intensive study. Much has been written that is obviously speculative in character, but gradually there is emerging considerable that is proven fact. It is the purpose of this article to review some of the pertinent literature on the clinical and electrocardiographic aspects of low basal metabolism and to report a study of the electrocardiographic findings in patients exhibiting a low rate of basal metabolism.

## CLINICAL LITERATURE

No mention is made of any endocrine disturbance in a series of well-known books on cardiac subjects (1, 2, 3, 4, 5). Others (6, 7) speak of the heart in goiter, but do not mention thyroid deficiency. Osler (8) says that the heart is normal in myxedema. Romberg (9) has one paragraph on myxedema heart. Hirschfelder (10) says that while symptoms of cardiac weakness are present in myxedema, they are not prominent features and are of little importance in connection with disease of the heart. Simple hypothyroidism is not mentioned.

The medical journals during the past fifteen years report a few investigations on this subject. Hertoghe (11) of Belgium in 1914 wrote an excellent paper describing the symptoms and treatment of a score or more myxedematous patients. He says that infiltration which is brought on by thyroid insufficiency causes the muscle cell to increase in size so that contraction is delayed in onset and slow in execution. This applies to both the involuntary and the voluntary muscle. The above explanation might well account for the flabby heart action noted by others.

Hertoghe goes on to say that the nutrition and excretion of the nerve cell is hindered. The transmission of motor, sensory, and voluntary impulses is delayed by infiltration of the cell itself and its supporting connecting tissues. As far as the heart is concerned, this may cause cardiac pain with radiations like those of angina. Dyspnoea is present, more or less markedly according to the severity of the myxedema.

Zondek (12) in 1918 pointed out the absence of medical literature on the heart in myxedema, and reported observations upon four patients with this disorder. He found the heart to be bilaterally dilated, often to a high degree, with indolent action, slow rate, normal blood pressure, and electrocardiographic changes. After thyroid medication he noted that the

heart returned to about the normal size, the action became vigorous, the rate increased moderately, and the blood pressure remained unchanged. The electrocardiogram gradually reverted to normal.

The following year, Assmann (13) reported a case of myxedema in which Zondek's clinical observations were repeated. Digitalis, diuretin, and theocin were without beneficial effect, but the later administration of thyroid therapy was entirely successful. Zondek (14) contributed a second article in 1919.

Meissner (15) reported three more cases of myxedema, confirming Zondek's observation of the dilatation, which receded after the resort to thyroid medication. Unfortunately no electrocardiograms were obtained from these patients in the untreated stage. A few more reports by other observers have been published, but since they concerned chiefly the electrocardiographic findings their enumeration will be deferred until the subsequent section of this article.

Fahr (16) believes heart failure is a prominent feature of all cases of myxedema, and that a mild degree of heart failure, with very slight dilatation of the heart, is not at all infrequent in women patients past the age of 45, exhibiting slight but definite evidence of hypothyroidism. He reports four cases with dilatation in all the heart chambers which improved under thyroid medication after failure to respond to digitalis.

Christian (17) and Willius and Haines (18) do not agree with Fahr's conclusions. Christian (17), among 32 cases of myxedema, found only 10 showing any cardiac disturbance, and none of these resembled the type described by Fahr.

Willius and Haines (18), from a study of 162 cases of myxedema, conclude that there is no characteristic heart failure nor cardiovascular disease in this disorder.

Fahr, in a later paper (19), again insists that the term "myxedema heart" is justified, since in myxedema, symptoms of heart failure are often found which are nearly or completely relieved by the administration of thyroid extract. He finds it hard to understand why Willius and Haines failed to find heart failure in the large number (162) of cases they report. (One wonders if these were all true myxedema cases or hyperthyroidism without myxedema.) He cites several reports in the German literature which agree with his findings; that is, myxedema cases with symptoms of heart failure which were relieved when the basal metabolism had returned to normal under thyroid medication. Fahr reports six cases in this paper in which like results were noted. One subject, previously reported, had been studied four years. Her cardiac symptoms returned whenever the thyroid medication was suspended or reduced to the point of giving a subnormal basal metabolic rate.

Lawrence (20) has pointed out that depressed basal metabolism means a depression of functional activity of all the organs concerned in furnishing energy and nutrition to the body. This leads to enfeebled heart beat. He makes a distinction between myxedema and thyroid failure without



myxedema, there being greater depression of cardiac function in the former. He says that the patient with myxedema tires easily when subjected to exercise tests, but the heart rate does not increase as much as does that of a normal subject.

Means (21) states that in myxedema the cardiac output per systole may be reduced 50 per cent, and that the blood flow and work of the heart are similarly diminished.

Sturgis (22) reports 15 myxedematous patients, but evidently did not think the heart an important factor, as he omits any data pertaining to cardiac conditions, although he gives a detailed statement of findings.

Means, White and Krantz (23) question whether there is an abnormality sufficiently characteristic to justify the term "myxedema heart," but say that the condition of the heart in myxedema is important. An occasional myxedematous patient presents a type of cardiac flabbiness which is truly due to his low metabolic level. They point out that myxedema predisposes to arteriosclerosis. This may cause damage, just as it does in non-myxedematous patients. Too free use of thyroid extract in cases in which arteriosclerosis is present is dangerous because a rapid rise in metabolism increases the work of the heart by increased blood flow and may overwork a sclerosed heart. Also it has been observed that in cases of angina pectoris with myxedema the anginal symptoms often become more severe as the rate of the basal metabolism is raised to normal. Therefore, in such cases, it is important to keep the metabolic level below that at which anginal symptoms occur.

Read (24) discusses pulse rate in relation to basal metabolic rate, and states that the pulse rate varies directly with the basal metabolic rate. Sturgis and Whiting (25) agree with him in thinking that the pulse rate is of value in giving an idea of the basal metabolism. Higgins (26) found the pulse rate below 70 in only a few cases, and in some a definite increase above normal. He explains this by the fact that milder grades of thyroid deficiency are generally associated with other pathologic conditions which may alter the pulse rate; an accelerated pulse may therefore exist in spite of hypothyroidism.

#### LITERATURE ON ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiograph has been used to a limited extent in studying patients with low basal metabolism, especially in cases of myxedema.

Zondek (12) apparently was the first investigator in this field. In his four cases of myxedema he found the P and T waves to be small or absent. After effective thyroid therapy these waves gradually reappeared, and if medication was pushed Zondek reported that the P and T waves may gradually assume an abnormal height. In his second contribution (14) Zondek reported that he used the reappearance of these waves as an indication for stopping the administration of thyroid therapy, and their diminution for resumption of the drug. This investigator also found the

heart and electrocardiogram to be normal in osteomalacia, the hypogonad state, infantilism, eunuchoidism and adiposogenital dystrophy.

Nobel, Rosenbluth and Samet (27) obtained the electrocardiograms of eleven children with myxedema and confirmed Zondek's findings in that the P and T waves were very small, sometimes absent. They then employed needle electrodes and took the current from the chest wall over the precordia. This procedure demonstrated the presence of normal P and T waves. These investigators, therefore, concluded that the abnormal electrocardiogram in myxedematous children is largely due to changed resistance in the skin, and thereby an expression of altered metabolism, but not of an abnormal mechanism of the heart. They explain the normal electrocardiograms in two of their patients (infants less than two years old) as due to the lessening of skin resistance in the very young.

These workers found the electrocardiogram to be normal in mongolian idiots.

Gardner (28) stated that he had examined the electrocardiograms of 275 patients with a low rate of the basal metabolism and found them normal save in myxedema. He does not, however, give a detailed analysis. It is clear from his article that he appreciates the fact that a low basal rate may be found in non-thyroid conditions. Gardner records six case histories of myxedema, but only a single electrocardiogram. In this he noted periods of marked auricular flutter, arborization block (so-called), and inversion of the T wave. These findings gradually returned to normal during a period of four years.

Thacher and White (29) report 14 cases of myxedema at the Massachusetts General Hospital. They believe that there is a distinct parallelism between the T wave of the electrocardiogram and the basal metabolic rate in hypothyroidism, the T wave being not more than 1 mm. in height in lead 2, instead of 2 mm. or more, as in the normal electrocardiogram. They found also a general decrease in potential of all deflections in all leads. They point out that low potential in all leads is found in myocardial exhaustion due to serious coronary sclerosis, a fact which appears to show that cardiac action is sluggish in myxedema. These 14 cases give an average heart rate of 68. There was no definitely abnormal axis deviation.

Thacher (30), in an earlier paper, found a low, flat, or inverted T in cretinism as well as myxedema. Mongolian idiots showed no electrocardiographic changes.

It has been shown (31) that the T wave of the electrocardiogram is modified by three factors: (1) Duration and order of excitation in the various fractions of the heart; (2) the relation of the anatomical axis to the recording electrodes; (3) the magnitude of the electrical resistance in the extra-cardiac tissues, especially that caused by polarization and capacity changes in the skin. A small or absent T wave associated with small initial complexes (QRS) found in myxedema and some other conditions may be

explained as the result of an increase in electrical resistance and capacity changes in the skin and tissues.

Willius and Haines (18), in their study of 55 cases, found electrocardiographic abnormalities which disappeared under thyroid medication. They note negative T waves in one or more of the three leads in 23 cases. An aberrant QRS was found in one case, delayed A-V conduction in one case, and one showed auricular fibrillation. Twenty-eight were normal.

Hamburger (32) and co-workers, in a study of 32 cases of thyroid disease, report changes in the T wave following iodine medication and thyroidectomy. They found that, in most instances, iodine medication resulted in diminution of the height of the T wave, while subtotal thyroidectomy was followed by even greater lowering. They concluded therefore that decrease in basal metabolic rate paralleled decrease in the height of the T wave in these cases.

White and Aub (33), on the other hand, found very limited parallelism between the basal metabolism and the amplitude of the T wave in a series of 27 cases of thyroid disease, but in hypothyroidism they found a low T wave which increased under treatment. In this paper, however, they record only 3 cases of low basal metabolism with T waves—0.25 mvt., 0.15 mvt. and 0, respectively.

Means, White and Krantz (23) found electrocardiographic changes involving the P wave, and low amplitude which disappeared after treatment. They do not state what they consider to be the height of the normal P wave. Fahr (16), reporting one patient only, finds a slightly atypical intraventricular block with low or flat T in all leads and a normal P. The  $QRS_3$  was negative, as one would expect with right bundle branch block. The block disappeared after thyroid medication, the QRS became positive, and the T wave became first diphasic and later normal. When thyroid medication was discontinued, the changes reappeared. Fahr says that the QRS may be split and wide, but this is less common than changes in the T wave. A negative  $QRS_3$  is found in severe cases with mild dilatation. In a later paper Fahr (19) reports that this patient, after six months of treatment with thyroid extract, reverted permanently to the split and prolonged QRS, despite a normal rate of basal metabolism.

Curshmann (34) was unable to confirm Zondek's findings in the electrocardiogram of patients with myxedema, and states he would not place the marked value on these signs as does Zondek.

Some significant experimental work has been reported by Lueg (35). He removed the thyroid gland from rabbits, dogs, sheep, and goats when young, and later found the P and T waves to be low (the so-called Zondek signs), and also a reversal of the ventricular complex. This investigator was able to change a normal electrocardiogram of either man or animal into one resembling that found in myxedema by using special electrodes (a few square millimetres of platinum). He measured the electrical capacity of the skin and found at certain levels the introduction of a con-

denser of 0.7 microfarads caused changes in the electrocardiogram. Lueg states that removal of the thyroid always causes a lessening of the value of the electrical capacity in the skin if a well-marked myxedema has appeared. He asserts that the changes in the electrocardiogram in myxedema are due to increased polarizability in the skin and believes that the electrical current lead off (*i. e.*, by the electrodes) from the body is no longer a true representative of the electrical changes in the heart.

#### PERSONAL STUDIES

The electrocardiographic data reported seemed of such interest and possible importance in diagnosis that we wished to investigate the subject further. The relatively small number of patients examined by most of the previous observers did not seem enough from which to draw conclusions. Therefore we have tried to assemble a large enough group of cases with low basal metabolism to show the frequency of the changes reported. Our study represents a total of 590 cases. We have compared the findings shown in the electrocardiograms of 260 cases with basal rates of from  $-10$  per cent to  $-48$  per cent, with those shown in the electrocardiograms of an equal number of patients whose basal metabolism was normal (between  $-10$  per cent and  $+10$  per cent) and 70 patients with a basal metabolism above normal (ranging from  $+10$  per cent to  $+96$  per cent).

*Results.* Our results show a low P wave (0.1 mvt. or less) in 96 of the 260 cases with low basal metabolism, as compared with 87 of the 260 cases with normal basal metabolism; a low T (0.1 mvt. or less) in 37 of the first group and in 46 of the second group; low R (less than 1.0 mvt.) is found in 50 of the first group as compared with 37 of the normal group (see Table I).

There is, therefore, no striking difference in the heights (voltage) of these three waves in the two groups, low P and low R being found slightly more often with a low basal metabolic rate, but low T more often in the normal group. A single low wave was found more often in the normal group, but 2 low waves were more frequent in the low basal group. Three low waves were found in 10 of the cases with low basal metabolism (2 being cases of real myxedema) and in only 3 of the normal group. Invert QRS in lead 3 was practically the same in both groups, being found 81 times in the normal and 83 times in the group of cases with low basal metabolism.\*

The cases diagnosed as hypothyroid show a slightly higher percentage of low waves than is shown in the whole group, which includes other endocrine disturbances. Among the cases of hypothyroidism were many with mild myxedema, but only six in which the myxedematous state was an outstanding feature. When the electrocardiograms of this small group of

\* Footnote.—Since we have been unable to find any statement in the literature quoted as to what constitutes a low P wave, we have classified as low all P waves not exceeding 0.1 millivolt in lead 2. Thacher and White (29) call a T low which does not exceed 0.1 millivolt in lead 2, and we have used this criterion in classifying the T wave as low.

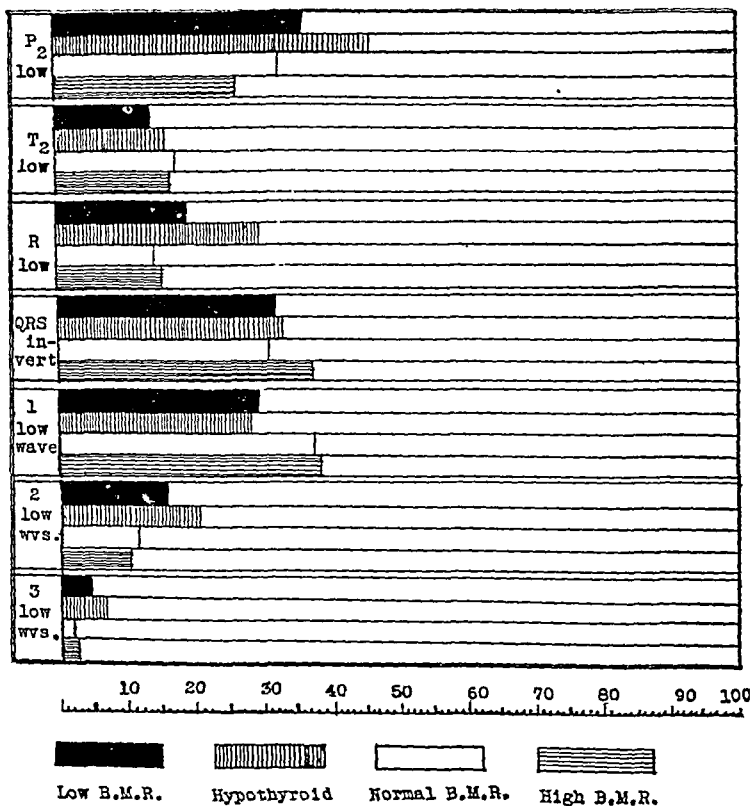
TABLE I

Comparison of the Electrocardiographic Findings in Hypothyroidism and in Low, Normal, and High Rates of Basal Metabolism

	Total Number	P <sub>2</sub> low %	T <sub>2</sub> low %	R low all leads %	QRS invert %	No sign %	No low wave %	1 wave low %	2 waves low %	3 waves low %
Hypothyroid*.....	80	41.3	16.3	30.0	32.5	32.5	45.0	28.8	20.0	6.2
Low B. M. R.....	260	34.2	14.2	19.2	31.9	39.2	52.8	29.2	15.0	3.8
Normal B. M. R.....	260	33.4	17.7	14.2	31.1	36.1	48.2	37.8	11.15	1.15
High B. M. R.....	70	27.1	17.2	15.7	34.1	37.1	51.5	33.6	10.1	1.5

\*Included in low B. M. R. group.

Plate 1 Illustrating Table I



marked myxedemics are analyzed, five show low P and T waves, three of these having R waves less than 0.5 mvt. and two, R waves measuring 1.0 millivolt in the lead giving the maximum deflection. The sixth case had been already treated and shows normal voltage, but invert T in leads 1 and 2. None of the six have an invert QRS in lead 3.

TABLE II

Analysis of Electrocardiographic Findings in Low Basal Metabolism

Diagnosis	No. in B. M. R. Group —10% to —20%	Showing Sign Indicated		No. in B. M. R. Group —21% to —30%	Showing Sign Indicated		No. in B. M. R. Group —31% to —40%	Showing Sign Indicated		B. M. R. —10% to —40% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
Hypothyroid	36	P <sub>2</sub> 1 mm. or less		30	P <sub>2</sub> 1 mm. or less		14	P <sub>2</sub> 1 mm. or less			Low P <sub>2</sub>	
Pituitary	51	12	33.3	23	11	36.6	1	10	71.5	80	33	41.3
Gonad.	18	14	27.5	3	10	13.6	1	1	100.	76	26	31.2
Unclassified Endocr.	27	5	27.8	3	0	0.	0	21	0.	21	5	23.8
Non-Endocrine	39	5	18.5	12	2	15.6	0	38	0.	38	7	18.4
		16	41.0	6	2	33.3	0	45	0.	45	18	40.0
Total	171	53	31.1	71	25	33.8	15	11	73.3	260	89	31.2
Hypothyroid	36	T <sub>2</sub> 1 mm. or less		30	T <sub>2</sub> 1 mm. or less		14	T <sub>2</sub> 1 mm. or less			Low T <sub>2</sub>	
Pituitary	51	3	8.3	23	2	6.7	1	8	57.2	80	13	16.3
Gonad.	18	5	9.8	3	2	8.7	1	0	0.	76	8	10.5
Unclassified Endocr.	27	1	5.6	3	0	0	0	21	0.	21	1	4.7
Non-Endocrine	39	3	11.1	12	2	16.6	0	38	0.	38	5	13.3
		8	20.5	6	2	33.3	0	45	0.	45	10	22.1
Total	171	21	12.5	71	8	10.8	15	8	53.4	260	37	14.2
Hypothyroid	36	All leads R less than 1 cm.		30	R less than 1 cm.		14	R less than 1 cm.			Low R	
Pituitary	51	11	30.6	23	6	10.0	1	7	50.0	80	24	30.0
Gonad.	18	7	13.7	3	2	8.7	1	0	0.	76	9	11.8
Unclassified Endocr.	27	3	16.6	3	1	33.3	0	21	0.	21	4	19.0
Non-Endocrine	39	3	11.1	12	2	16.6	0	38	0.	38	5	13.3
		6	15.1	6	2	33.3	0	45	0.	45	8	17.8
Total	171	30	17.5	71	13	17.5	15	7	46.6	260	50	19.2
Hypothyroid	36	Negative QRS <sub>2</sub>		30	Negative QRS <sub>2</sub>		14	Negative QRS <sub>2</sub>			Negative QRS <sub>2</sub>	
Pituitary	51	12	33.3	23	12	10.0	1	2	11.2	80	26	32.5
Gonad.	18	13	33.3	3	1	17.1	1	0	0.	76	22	28.9
Unclassified Endocr.	27	5	27.8	3	1	33.3	0	21	0.	21	6	28.8
Non-Endocrine	39	6	22.2	12	5	11.7	0	38	0.	38	11	29.0
		15	38.1	6	3	50.0	0	45	0.	45	18	40.0
Total	171	56	32.7	71	25	33.8	15	2	13.3	260	83	31.9
Hypothyroid	36	None of the above		30	None of the above		14	None of the above			None of the above	
Pituitary	51	12	33.3	23	13	13.4	1	1	7.1	80	26	32.5
Gonad.	18	21	17.1	3	11	17.8	1	0	0.	76	35	46.0
Unclassified Endocr.	27	9	50.0	3	1	33.3	0	21	0.	21	10	47.7
Non-Endocrine	39	14	51.7	12	1	33.3	0	38	0.	38	18	47.7
		12	30.8	6	1	16.6	0	45	0.	45	13	28.9
Total	171	71	41.5	71	30	40.5	15	1	6.7	260	102	39.2
Hypothyroid	36	No low wave		30	No low wave		14	No low wave			No low wave	
Pituitary	51	16	11.5	23	19	63.4	1	1	7.1	80	36	45.0
Gonad.	18	33	61.8	3	12	52.3	1	0	0.	76	45	59.2
Unclassified Endocr.	27	11	61.2	3	2	66.6	0	21	0.	21	13	61.9
Non-Endocrine	39	18	66.7	12	6	50.0	0	38	0.	38	21	63.3
		17	43.5	6	2	33.3	0	45	0.	45	19	42.2
Total	171	95	55.6	71	41	55.1	15	1	6.7	260	137	52.8
Hypothyroid	36	1 low wave		30	1 low wave		14	1 low wave			1 low wave	
Pituitary	51	15	41.7	23	3	10.0	1	5	35.7	80	23	28.8
Gonad.	18	11	27.5	3	8	31.8	1	1	100.	76	23	30.3
Unclassified Endocr.	27	5	27.8	3	1	33.3	0	21	0.	21	6	28.8
Non-Endocrine	39	5	18.5	12	4	33.3	0	38	0.	38	9	23.6
		12	30.8	6	3	50.0	0	45	0.	45	15	33.3
Total	171	51	29.9	71	19	25.7	15	6	40.0	260	76	29.2
Hypothyroid	36	2 low waves		30	2 low waves		14	2 low waves			2 low waves	
Pituitary	51	4	11.1	23	8	26.6	1	4	28.6	80	16	20.0
Gonad.	18	3	5.9	3	3	13.0	1	0	0.	76	7	9.2
Unclassified Endocr.	27	2	11.1	3	0	0	0	21	0.	21	2	9.5
Non-Endocrine	39	3	11.1	12	2	16.6	0	38	0.	38	5	13.3
		9	23.0	6	0	0.	0	45	0.	45	9	20.0
Total	171	22	12.8	74	13	17.5	15	4	26.6	260	39	15.0

TABLE II—Cont.

Diagnosis	No in B M R Group —10% to —20%	Showing Sign Indicated		No in B M R Group —21% to —30%	Showing Sign Indicated		No in B M R Group —31% to —40%	Showing Sign Indicated		B M R —10% to —40% Totals	Showing Sign Indicated	
		No	%		No	%		No	%		No	%
Hypothyroid	36	3 low waves		30	3 low waves		14	3 low waves		80	3 low waves	
Pituitary	51	1	2 8	23	0	0	1	4	28 6	76	5	6 2
Gonad	18	2	3 9	3	0	0	0	0	0	21	2	2 6
Unclassified Endocr	27	0	0	12	0	0	0	0	0	38	0	0
Non-Endocrine	39	1	3 7	6	1	16 6	0	0	0	45	1	2 6
Total	171	5	2 9	74	1	1 3	15	4	26 6	260	10	3 8
Hypothyroid	36	Pulse Av		30	Pulse Av		14	Pulse Av		80	Pulse Av	
Pituitary	53	71 0		23	70 7		1	69 7		76	72 0	
Gonad	18	79 0		3	74 7		0	75 0		21	77 5	
Unclassified Endocr	27	78 7		12	71 6		0			38	77 7	
Non-Endocrine	39	72 7		6	75 7		0			45	73 6	
Total	171	77 2			81 5						79 6	

Plate II Illustrating Table II

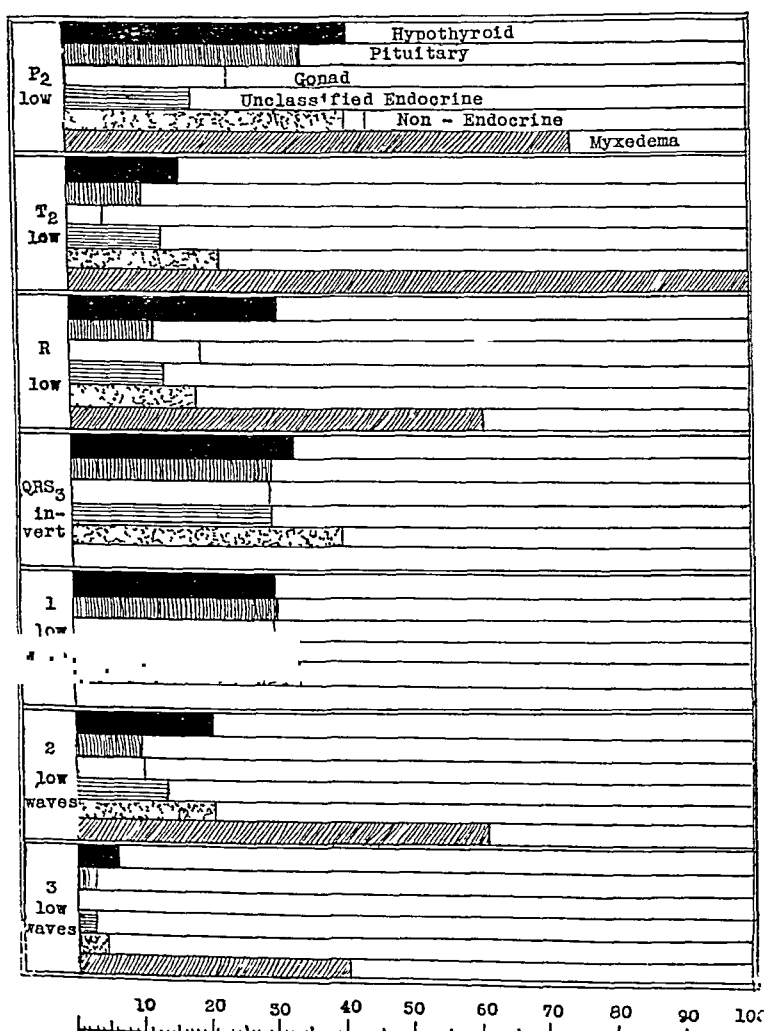


TABLE III  
Analysis of Electrocardiographic Findings in High Basal Metabolism

Diagnosis	No. in B. M. R. Group +10% to +20%	Showing Sign Indicated		No. in B. M. R. Group +21% to +40%	Showing Sign Indicated		No. in B. M. R. Group +41% to +96%	Showing Sign Indicated		B. M. R. +10% to +96% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
		P <sub>2</sub> 1 mm. or less			P <sub>2</sub> 1 mm. or less			P <sub>2</sub> 1 mm. or less			Low P <sub>2</sub>	
Hyperthyroid.....	1*	0	0.	8	2	25.0	11	3	27.3	23	5	21.7
Muscl. & Unclas. End.	12	4	33.3	3	0	0.	1	0	0.	16	4	25.0
Non-Endocrine.....	20	6	30.0	9	3	33.3	2	1	50.0	31	10	32.3
Total.....	36	10	27.8	20	5	25.0	14	1	28.6	70	19	27.1
		T <sub>2</sub> 1 mm. or less			T <sub>2</sub> 1 mm. or less			T <sub>2</sub> 1 mm. or less			Low T <sub>2</sub>	
Hyperthyroid.....	1*	0	0.	8	0	0.	11	0	0.	23	0	0.
Muscl. & Unclas. End.	12	1	8.3	3	1	33.0	1	0	0.	16	2	12.5
Non-Endocrine.....	20	1	20.0	9	6	66.0	2	0	0.	31	10	32.3
Total.....	36	3	13.8	20	7	35.0	14	0	0.	70	12	17.2
		R less than 1 cm.			R less than 1 cm.			R less than 1 cm.			Low R	
Hyperthyroid.....	1*	1	25.0	8	0	0.	11	0	0.	23	1	4.3
Muscl. & Unclas. End.	12	1	33.3	3	1	33.3	1	0	0.	16	5	31.3
Non-Endocrine.....	20	3	15.0	9	1	11.1	2	1	50.0	31	5	16.1
Total.....	36	8	22.2	20	2	10.0	14	1	7.1	70	11	15.7
		Negative QRS <sub>2</sub>			Negative QRS <sub>2</sub>			Negative QRS <sub>2</sub>			Negative QRS <sub>2</sub>	
Hyperthyroid.....	1*	2	50.0	8	3	37.5	11	3	27.3	23	8	24.8
Muscl. & Unclas. End.	12	1	33.3	3	3	100.0	1	0	0.	16	7	43.7
Non-Endocrine.....	20	5	25.0	9	3	33.3	2	1	50.0	31	9	29.1
Total.....	36	11	30.6	20	9	45.0	14	4	28.6	70	24	34.1
		None of the above			None of the above			None of the above			None of the above	
Hyperthyroid.....	1*	1	25.0	8	5	62.5	11	7	63.6	23	13	56.6
Muscl. & Unclas. End.	12	3	25.0	3	0	0.	1	1	100.0	16	4	25.0
Non-Endocrine.....	20	7	35.0	9	1	11.1	2	1	50.0	31	9	29.1
Total.....	36	11	30.6	20	6	30.0	14	9	64.3	70	26	37.1

\*Of these four cases, one only was diagnosed as true hyperthyroid. One was a case of goiter with possible hyperthyroidism, in one the diagnosis was toxic thyroidosis, and in the other thyroid dysfunction.

The group with high basal metabolism shows a higher percentage of low T waves in lead 2 than does either the entire low group or the hypothyroid group, but low P in lead 2 and low R (all leads) are not found as often, though the difference is not great. A negative QRS in lead 3 is found slightly more often in the high than in either of the low groups.

These comparisons will be made clearer by a study of Table I. Table II shows the entire group of low basal metabolic cases analyzed according to diagnosis and rate of basal metabolism, and Table III compares the high basal metabolic group in like manner.

*T Wave.* Willius and Haines (18) reported a negative T wave in one or more leads in 23 of their 55 cases. The occurrence of T and S-T changes in our electrocardiograms is shown in Table IV.

#### PERCENTAGE T AND S-T CHANGES

These figures show that invert T and S-T changes are not found more often in the group with low basal metabolism than in either of the other



TABLE III

Analysis of Electrocardiographic Findings in High Basal Metabolism

DIAGNOSIS	No. in B. M. R. Group +10% to +20%	Showing Sign Indicated		No. in B. M. R. Group +21% to +40%	Showing Sign Indicated		No. in B. M. R. Group +41% to +96%	Showing Sign Indicated		B. M. R. +10% to +96% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
Hyperthyroid.....	4*	No low wave		8	No low wave		11	No low wave		23	No low wave	
Misc. & Unclass. End.	12	3	75.0	3	6	75.0	1	3	75.5	17	6	74.0
Non-Endocrine.....	20	4	33.3	9	1	33.3	2	1	100.0	16	13	37.4
Total.....	36	10	50.0	20	2	22.2	2	1	50.0	31	13	41.9
Hyperthyroid.....	4*	1 low wave		8	1 low wave		11	1 low wave		23	1 low wave	
Misc. & Unclass. End.	12	1	25.0	3	2	25.0	1	3	27.3	16	9	26.1
Non-Endocrine.....	20	7	58.3	9	2	66.6	2	0	0.	31	12	56.0
Total.....	36	8	35.0	20	5	55.5	2	0	0.	31	12	38.8
Hyperthyroid.....	4*	2 low waves		8	2 low waves		11	2 low waves		23	2 low waves	
Misc. & Unclass. End.	12	0	0.	3	0	0.	1	0	0.	16	0	0.
Non-Endocrine.....	20	2	16.6	9	0	0.	2	0	0.	31	2	12.5
Total.....	36	3	15.0	20	1	11.1	2	1	50.	31	5	16.1
Hyperthyroid.....	4*	3 low waves		8	3 low waves		11	3 low waves		23	3 low waves	
Misc. & Unclass. End.	12	0	0.	3	0	0.	1	0	0.	16	0	0.
Non-Endocrine.....	20	0	0.	9	0	0.	2	0	0.	31	1	3.2
Total.....	36	0	0.	20	0	0.	14	0	0.	70	1	1.5
Hyperthyroid.....	4*	Pulse Av.		8	Pulse Av.		11	Pulse Av.		23	Pulse Av.	
Misc. & Unclass. End.	12	107		3	109		1	114		16	111	
Non-Endocrine.....	20	87		9	110		2	160		31	95.9	
Total.....	36	89		20	83		2	133		31	90.0	

\*Of these four cases, one only was diagnosed as true hyperthyroid. One was a case of goiter with possible hyperthyroidism, in one the diagnosis was toxic thyroidosis, and in the other thyroid dysfunction.

TABLE IV

Percentage T and S-T Changes

GROUP	No change	T <sub>1</sub> only	T <sub>1</sub>	-T 2 leads	-T 3 leads	S-T change
Normal.....	48.2	35.0	2.7	5.0	0.38	7.7
Low.....	55.7	36.5	0.77	2.3	0.38	6.1
High.....	60.0	24.3	2.86	5.7	2.86	7.1

groups. These changes, except for invert T in lead 3 (often not considered abnormal) were infrequent in any group.

*Rhythm.* As to rhythm, of the 260 low basal metabolic cases, 220 showed normal rhythm or sinus arrhythmia, 15 simple tachycardia and 15 normal rhythm with premature beats. Only 10 showed any significant arrhythmia, 8 being partial auriculo-ventricular block (P-R greater than 0.21 second) and 2 intraventricular block. Ninety-three had pulse rates not exceeding 70 per minute.

Of the 260 subjects with normal basal metabolic rates, 210 showed normal conditions or sinus arrhythmia, 29 simple tachycardia, 9 normal with premature beats, and 12 arrhythmia, of which 7 were partial auriculo-ventricular block, 3 intraventricular block, and 2 auricular fibrillation.

Fifty-two had pulse rates not exceeding 70.

It is evident that delayed conduction, either auriculo-ventricular or intraventricular, does not parallel low basal metabolism, since its occurrence is practically the same in both the above groups.

The rhythms found among the 70 cases of high basal metabolism were as follows: Thirty-four normal or sinus arrhythmia, 27 simple tachycardia, 4 simple tachycardia with premature beats, 2 normal with premature beats, 1 paroxysmal tachycardia, and 2 auricular fibrillation. Five had pulse rates not exceeding 70. It will be noted that conduction defects were not present in this group.

It has been stated that the electrocardiogram reverts to normal as the low basal rate rises to normal during thyroid therapy.

A second tracing was obtained in 14 cases after treatment with thyroid extract. Four showed no change in basal rate and no change in the voltage of the electrocardiographic waves. Three, which had a basal rate from 11 to 20 per cent higher in the second test, showed no change in the electrocardiogram. One subject of myxedema, whose basal metabolic rate went from  $-39$  to  $-3$ , showed marked increase in voltage. A pituitary dysfunction case showed marked increase in basal rate with slight increase in voltage.\* In one case the basal metabolic rate dropped from  $-22$  per cent to  $-33$  per cent, but there was no change in the electrocardiogram. Another subject whose basal rate dropped from  $-7$  to  $-20$  had lower voltage in the second electrocardiogram. Two others, in spite of a slightly higher basal rate showed slightly lower waves. One with an increase in basal rate of only 2 per cent showed slight increase in voltage.

In brief, then, in the 5 cases in which the basal rate was definitely higher (at least 11 per cent) at the time of the second electrocardiogram, in only 2 was the voltage higher, while in the three others it remained unchanged.

#### COMMENT

One of the articles on the electrocardiogram in myxedema which first came to our attention states: ". . . There is a distinct parallelism between the T wave of the electrocardiogram and the basal metabolic rate in hypothyroidism" (29). This did not agree with our experience and our contact with endocrine patients, the study of whom is the chief work of this institution (The Evans Memorial), made us aware of the difference between

\* Footnote.—This was an artificial stimulation by the administration of thyroid extract. The electrical resistance at the time of the second electrocardiogram was found to be double that recorded at the first. This may have affected the voltage. It is emphasized that in comparing the voltage in different electrocardiograms, care should be taken to record the electrical resistance present when each tracing is taken. As pointed out by Kitz, to whom we have referred above, the magnitude of the electrical resistance is a significant factor in the voltage of the T and other waves. It is part of our routine technique to record the electrical resistance and to photograph the standardization in each electrocardiogram.

hypothyroidism with myxedema and without the latter. Many of the reports quoted in the literature we have reviewed do not contain evidence of making this distinction. It seems probable that this very fact accounts for the diversity of the opinions on the heart in myxedema.

It is worthy of note that Fahr reported but six cases of myxedema, and stated that these were all that were found in a period of six years in the General and University Hospitals in Minneapolis. It is not surprising, therefore, that our group collected in the course of three years numbers but six patients. No one who has found the cardiac findings in myxedema as first described by Zondek, reports more than a small number of cases.

The author of the most recent report (36) expresses the opinion that there are probably two groups of cases of myxedema heart: those in which thyroid medication is followed by restoration to normal and those in which it is not. Perhaps the development of arteriosclerotic changes, to which myxedema predisposes, is the reason, for the permanency of the abnormal findings.

#### SUMMARY

It has been reported by various observers that patients having a low rate of basal metabolism show certain characteristic signs in the electrocardiogram. These signs are: A low P wave in lead 2; low R in all leads; a low T in lead 2; inverted T in one or more leads; delayed auriculo-ventricular conduction; and spread and notched QRS. An estimate of the reliability of these electrocardiographic signs was undertaken on a somewhat larger series of patients than had hitherto been reported.

A study of 260 low basal metabolic cases, 260 normal basal metabolic cases, and 70 high basal metabolic cases showed that the above changes were not frequent enough in the first group to be called characteristic of low basal metabolism. More than half these cases showed no low wave and only 3.8 per cent showed low potential in all three leads. The cases diagnosed as hypothyroid showed a slightly higher percentage of low voltage curves, but even in this group, nearly half showed no abnormally low waves. The findings in the group with normal and in the group with high basal metabolism were not conspicuously different. Invert QRS was practically the same in all four groups. Delayed conduction, either auriculo-ventricular or intraventricular, was found only infrequently. Invert T and S-T changes were not more frequent in the group with low basal metabolism than in the groups with normal or high basal metabolism. In the five untreated cases of myxedema, all showed low T waves, and four showed low P waves as well. R waves less than 0.5 millivolt were found in three cases, and in each of the remaining two the R wave equalled 1.0 millivolt.

In conclusion, then, no electrocardiographic findings characteristic of low basal metabolism were found in this study of 590 cases. The definitely myxedematous subjects, on the other hand, showed the changes described by other investigators.

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# STUDIES ON OXYTOCIN AND VASOPRESSIN: PRESSOR ACTION\*†

L. W. ROWE, M.S.

The pressor action of posterior pituitary extracts was first commented on by Oliver and Schafer (1) in 1895. The tolerance caused by large, frequently repeated, intravenous doses was noted by Howell (2) in 1898. The quantitative pressor response of a deeply anesthetized dog (Chloretone preferably) to small, infrequently repeated (not oftener than every 15 to 20 minutes) doses of pituitary extract was the basis of the earlier standardization of the first commercial preparation (Pituitrin, 1909) though the method was not published by Hamilton (3) until 1912. Largely due to the use of modifications of the proposed pressor technique the results obtained by other workers were not so satisfactory and the oxytocic test proposed by Dale and Laidlaw (4) in 1912 found favor as the method of standardization. This method seemed more logical because of the clinical use of the product in obstetrics and was recommended in the U. S. P. X in spite of the admitted difficulties attendant upon its successful application and its large experimental error (20 to 25 per cent). English workers represented chiefly by Hogben, Schlapp and Macdonald (5, 6, 7, 7A) have published extensive experimental work on the pressor effects in the spinal cat but the technique is much more elaborate than that with the chloretonized dog and the accuracy is certainly no greater.

The recent separation of two active principles—a pressor and an oxytocic principle—from pituitary extract by Kamm, Aldrich, Grote, Rowe and Bugbee (8) proves the necessity for the use of a pressor method of standardization as well as the oxytocic method. For that reason some of the results of about 20 years' experience with the pressor method in this laboratory together with pressor experiments with the separated principles will be detailed in the hope that some of the difficulties encountered by others may be solved and a basis for a more universally acceptable pressor method may be reached.

## THE PRESSOR TECHNIQUE

Since this was first described (3) and later defended in 1916 by Hamilton and Rowe (9) further experience over a period of twelve years has only served to strengthen our belief in the necessity of using a pressor method and in the relative accuracy and practicability of our present technique. Closely following this publication (9) further experience with the oxytocic method gave more favorable results and for fully ten years both methods have been in constant use in this laboratory.

\*Contribution from the Medical Research Laboratories of Parke, Davis & Co., Detroit, Michigan.

†The names under which these active principles are now available are Pitocin and Pitressin, respectively.

Healthy dogs, preferably of medium size and short-haired, are completely anesthetized by chloretone. A 40 per cent solution of chloretone in 40 per cent alcohol is injected intraperitoneally, using about 1 cc. per kgm. body weight [for details see article on chloretone anesthesia (10)]. This gives a deep, steady, lasting anesthesia with a lowered blood pressure but one which responds quantitatively and, in most animals, to a satisfactory degree. Small doses corresponding to 0.04 cc. (1 cc. of a 1 to 25 dilution) of U. S. P. X standard pituitary extract are given intravenously not oftener than every 15 minutes and the rise in blood pressure recorded on a kymograph from one of the carotid arteries. The first reaction on any animal should usually be disregarded as it does not entirely agree with succeeding reactions from the same dose. Comparison of the quantitative pressor action produced by the doses of "standard" and "unknown" on the same animal at alternate intervals will ultimately give two sets of equivalent reactions which complete the pressor assay of the unknown. Adjustment to 100 per cent potency and a second assay complete the pressor standardization of the preparation.

#### PRESSOR STANDARD

The almost universal adoption of the international unit of oxytocic activity indicates the need of an analogous pressor unit. In our first publication on the separated principles (8) we suggested in a preliminary way a pressor standard such that standard pituitary extract U. S. P. X would contain 10 pressor units per cc. and standard desiccated posterior lobe U. S. P. X would contain 2 pressor units per mgm.

This subject was carefully considered at the meeting of the Health Committee of the League of Nations held at Frankfort, April 25th to 28th, 1928, and the following statement was made: "The Commission further recommends that the activity of any such preparation should be expressed in relation to the international standard in units of *pressor* or *oxytocic* activity, and that, in each case, *the unit of such activity* shall be that of 0.5 mgm. of the standard powder." The adoption of this logical pressor unit by such an international body would seem to place the final stamp of approval upon it as a means of stating definitely pituitary potency of this type.

In my experience of fifteen years with this method it has frequently happened that as many as 25 or 30 quantitative reactions have been obtained from one animal without the slightest evidence of tolerance or of depressor action. These have been the objections voiced by critics of the pressor method and, in my opinion, they are due to an insufficient depth of anesthesia as well as an insufficiently lowered blood pressure. With ether or chloroform anesthesia or even with incomplete chloretone anesthesia I have often seen the depressor effect which precedes the pressor and this detracts from the accuracy of the test. With such conditions prevailing neither the depressor nor the pressor action of a given dose can be

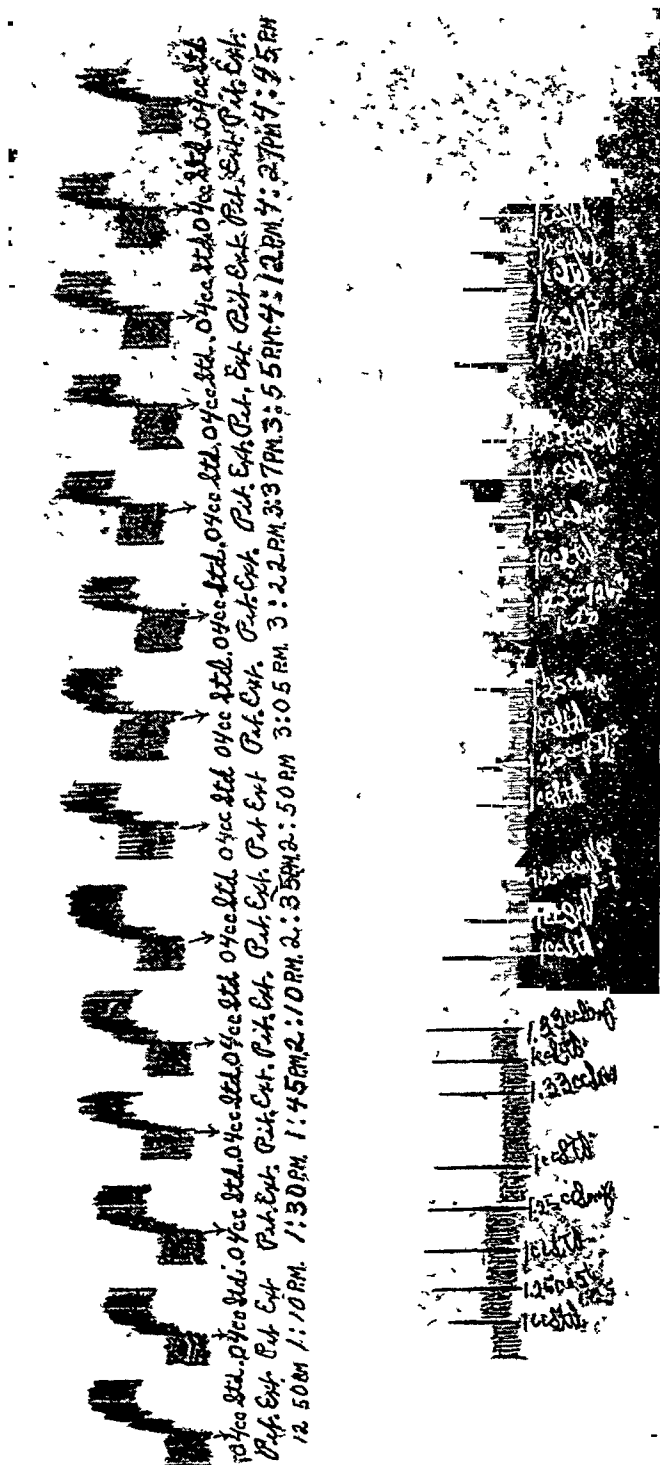


Figure 1. Above, partial detail of 14 successive standard doses. Below, abbreviated reactions for routine pressor tests





tocin under light and deep chloretone anesthesia. It will be noted that with the first four reactions the anesthesia was so light and the blood pressure so high that small doses produced only a slight pressor action and in two cases this was preceded by a slight depressor action. Later with the same animal under deep chloretone anesthesia there was no tendency to depressor action, even with large doses, though there was a marked development of tolerance due to the large doses.

This depressor action of pituitary extract under certain test conditions has been the subject of concern to many pharmacologists. Since histamine in very small amounts produces such a marked fall in the blood pressure of an anesthetized dog it was natural to assume that this depressor action might be due to histamine. Such depressor action which is frequently encountered is not characteristic of ordinary doses of fresh pituitary extracts and is not produced under conditions where histamine in very small amounts will produce a marked depressor effect.

This alone would rule out histamine as the cause of the depressor action which can be produced either by pituitary extracts or very large doses of oxytocic fraction.

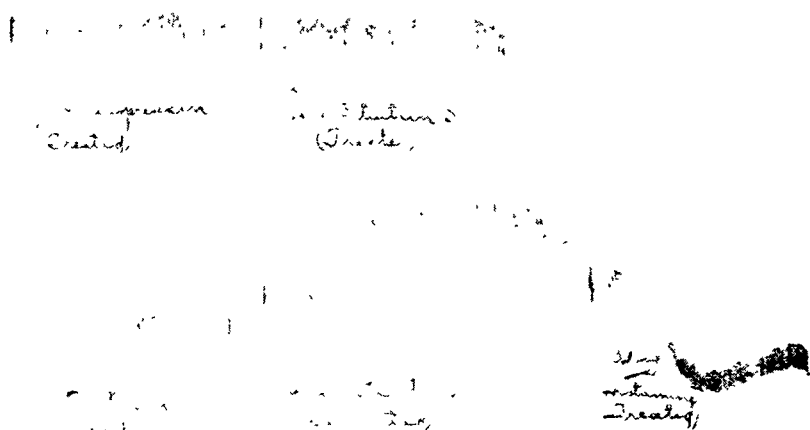


Figure 3. Rather large doses of Pituitrin, Vasopressin, Oxytocin and Histamine after treatment with sodium hydroxide. Also small dose of Pituitrin before treatment.

As a further proof of the absence of histamine in these fractions potent solutions were treated with strong sodium hydroxide solution (2N.) for at least one hour with the result that both the pressor and oxytocic activities were totally destroyed (see Fig. 3). Histamine hydrochloride in a 1 to 10,000 solution when similarly treated was still active as a depressor and oxytocic agent. There is another more logical explanation of the depressor action and that is the excess acid. Ordinary pituitary extracts contain 0.25 per cent free acetic acid and Fig. 4 shows the depressor action of 2 cc. of undiluted pituitary extract compared with that caused by 2 cc. of 0.25 per cent acetic acid on a dog anesthetized with ether. Abel (12) produced a marked depressor effect on an etherized cat with a very

large dose (8.75 mgm. in 2 cc.) of his highly purified tartrate. The blood pressure was abnormally high when the second and larger dose was given and the excess acid was evidently stronger than the pressor principle.

Tolerance to Vasopressin can be developed just as to Pituitrin with improper technique. Small doses repeated too frequently will produce such a result even in an animal that is properly anesthetized. Figs. 4 and 5 show the tolerance from large and small doses of both Pituitrin and Vasopressin under chlorotone and ether anesthesia and the lack of tolerance with small doses and proper anesthesia.

It will be noted from Fig. 4 that a small dose of Pituitrin and Vasopressin first produced a marked rise in blood pressure while a rather large dose of Oxytocin produced a very small pressor effect. Later when larger doses were given more frequently tolerance developed so rapidly that 100

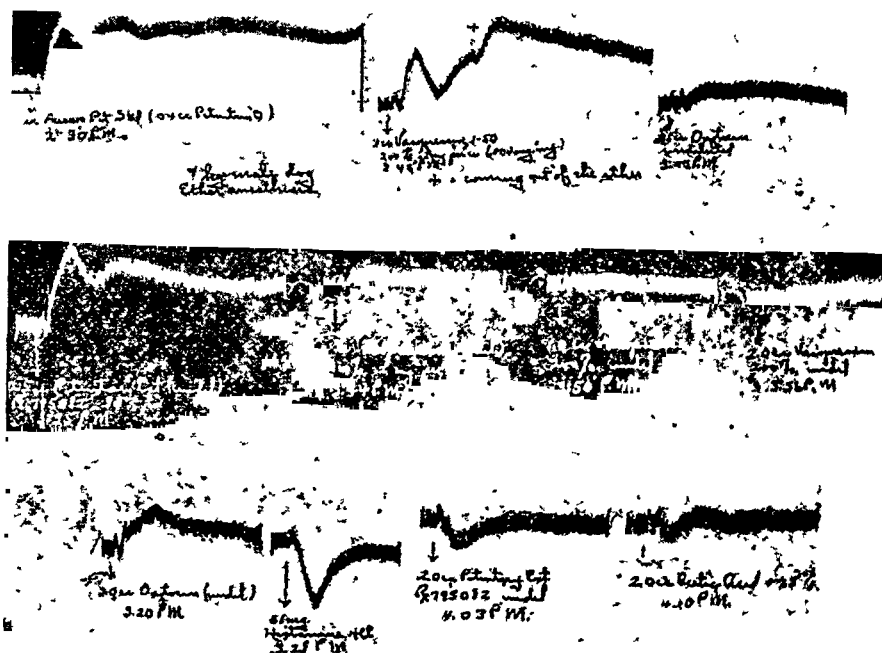


Figure 4. Pressure action with dog under ether. Tolerance from large doses of pressure action from Pituitrin and acid.

times as much Vasopressin produced no pressor effect though it also produced no depressor effect. Histamine still produced a marked and characteristic depressor effect.

Figure 5 shows the consistency of pressor response in No. 2 to No. 7 after No. 1 was a little greater than the rest. No. 8 to No. 12 show a definite degree of tolerance from the same small doses repeated every 10 minutes instead of every 15 or 20 minutes. No. 13 shows the return to normal reaction after a 20-minute rest. No. 14 to No. 18 show a still smaller response from the same small dose given every 5 minutes. No. 19 to No. 23 show the tolerance to large doses of Vasopressin when these are given too frequently. No. 25 is the result of a large dose of Oxytocin and

shows little, if any, depressor or pressor action. No. 25 is the characteristic depressor effect from a very small dose (0.1 mgm.) of histamine.

The use of different anesthetics such as ether, chloralose, etc., has been tried and it seems apparent that not quite as great a degree of accuracy can be expected with the animal under these anesthetics as under chloretone. A deep, steady and safe anesthesia could not be maintained with these anesthetics and even when the anesthesia was fairly deep the blood pressure was not low enough to prevent an occasional depressor reaction.

# SUMMARY

1. The pressor action of Vasopressin (the pressor principle of posterior pituitary extract—now Pitressin) is shown to be entirely similar to that of an active extract.

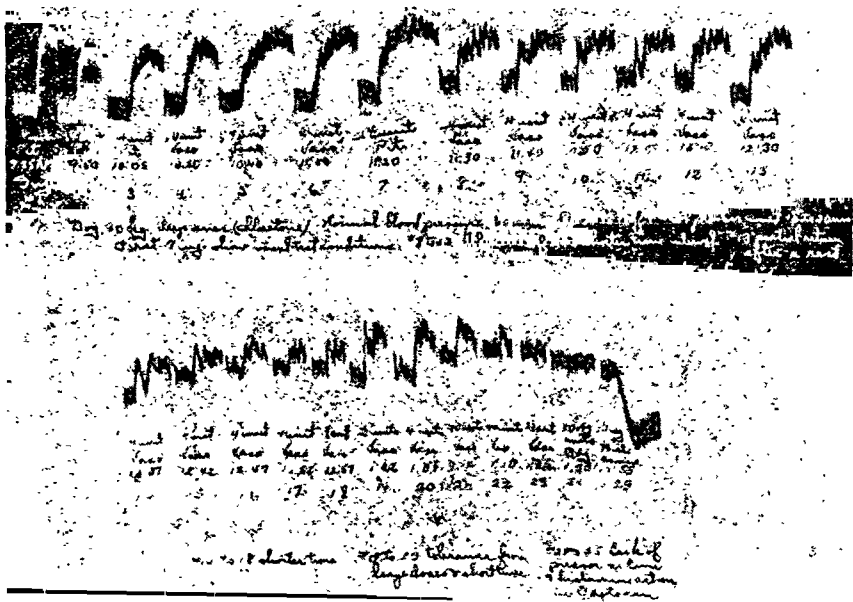


Figure 5. Lack of tolerance (1 to 7). Tolerance short time (8 to 12), large doses (19 to 23). Lack of pressor or depressor in large dose of Oxytocin.

2. The pressor action of Oxytocin (the oxytocic principle of posterior pituitary extract—now Pitocin) is shown to be chiefly due to the presence of the very small amount of unseparated vasopressin.

3. Neither vasopressin nor oxytocin produces a depressor action under proper test conditions.

4. Evidence is submitted to show the absence of an appreciable amount of histamine in either vasopressin, oxytocin or pituitrin.

5. Tolerance to vasopressin as to pituitrin can be produced with large or even small doses injected too frequently and lack of tolerance can also be shown with proper test conditions.

6. The technique of a pressor method which has proven satisfactory and practical as a quantitative index of pressor potency of pituitary extracts over a period of 20 years is again given in detail and suggested for adoption as the standard method of assay for this type of pituitary activity.

7. A pressor unit is defined which is logical and analogous to the international oxytocic unit. This pressor unit was suggested previously and was tentatively adopted at the recent Frankfort conference of the Health Committee, League of Nations.

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# Book Reviews

THE SIMPLE GOITER. Robert McCarrison. William Wood & Company, New York.

Reviewed in Arch. Int. Med. 42:607-608. 1928.

HORMONE UND INNERE SEKRETION. Fritz Laquer. Theodor Steinkopff, Dresden und Leipzig. 1928. Pp. 136.

The size of this little volume gives no hint as to its extensive content and the laborious effort involved in its production. A chapter is devoted to each of the recognized endocrine glands. This includes a short historical background, the hormone and its physiological effects and the clinical picture of dysfunction. The literature, as far as the author considers it significant, is brought down to date by some twelve hundred citations. In general this includes the work done since 1922. Careful reading of this volume will give a birdseye view of the general field of endocrinology and a new appreciation of its extent. In a volume of this nature the value of the work would be increased if the titles of the papers were included in the bibliography.

ENDOKRINE KRANKHEITEN. Hans Curschmann. Theodor Steinkopff, Dresden und Leipzig. 1927. Pp. 151.

The purpose and extent of this volume is best stated by the author in his preface. A free translation follows.

This small book will not and cannot exhaust the extensive literature. For that purpose voluminous handbooks are available now. It will, however, give clinical pictures of the more common endocrine diseases based upon a relatively large number of peculiar cases which with due consideration of the theoretical gives to the practical art that which is to it the most important—pathology, symptomatology and therapy.

The author describes the more common endocrine diseases in the usual manner and illustrates a number of them with photographs of his own patients.

THE COMPARATIVE PHYSIOLOGY OF INTERNAL SECRETION. Lancelot T. Hogben. The Macmillan Company, New York; The University Press, Cambridge, England. 1927. Pp. 148.

While not nearly as concentrated or extensive as Laquer, this little volume presents the more conspicuous features of the endocrine situation

to date. The usual method of discussing the subject gland by gland is avoided. Physiological activity is used as a basis for chapter division, e. g., "Chemical Coordination," "Endocrine Factors in Metabolism," etc. This volume will appeal to the lay reader since it has no clinical pictures, diagnostics or therapeutics. It is well worth careful reading.

# Abstract Department

**Failure to respond to adrenin in different types of failure and death of the heart.** (*Résistance à l'adrénaline par rapport aux divers processus de la mort du coeur*). Bardier, E., *Compt. rend. Soc. de biol.* **98**: 1408. 1928.

The dying heart fails in different ways, through muscular weakness, sudden spasm of the ventricles, or fibrillation. In dogs, it can be shown that in cases of over dosage of chloroform or of asphyxia the heart responds feebly or fails entirely to respond to injections of adrenin. These are cases where the heart fails slowly through muscular weakness.—J. C. D.

**Neural and hormonal factors in bodily activity. The prepotency of medulliadrenal influence in emotional hyperglycemia.** Britton, S. W., *Am. J. Physiol.* **86**: 340. 1928.

Normal cats which have been excited (while caged and displaying only minor muscular activity) by an aggressive dog show marked increments in blood-sugar level. Following two minutes' excitement the glycemic percentage is commonly augmented 30 to 90 per cent; greater increases (up to over 100 per cent) are observed after four minutes' excitation. The hyperglycemic as well as the general reactions become less marked with succeeding emotive responses. Evidences of parallelism in visceral and somatic responses are apparent. Hyperglycemia attending emotional reactions in animals with splanchnic branches to the liver severed and normal medulliadrenal function maintained is only slightly modified from the normal. Profound disability of the glycogenolytic mechanism is observed in animals which have been deprived of the adrenal medulla; emotional excitation for two or four minutes in such cases usually results in significant depressions in blood sugar which may persist for twenty minutes or longer. The general affective response is not appreciably altered. The hepatic glycogen in medulliadrenalectomized animals was within the normal limits. The observed emotional hypoglycemia, therefore, was probably referable to failure to mobilize glycogen, in the absence of adrenin secretion, adequately to supply the demands of even minor muscular activity. The importance of medulliadrenal intervention in calling forth readily available fuel for muscular activities during conditions of urgency is pointed out.

—Author's Summary.

**Suprarenal-renal heterotopia.** Caylor, H. D., *J. Urol.* **20**: 197. 1928.

Suprarenal-renal heterotopia is the developmental inclusion of cortical and medullary suprarenal tissue beneath the capsule of the kidney. All or only a part of the suprarenal gland may be beneath the renal capsule. The condition is frequently bilateral, it affects males chiefly, and it is usually associated with a thymicolymphatic constitution. The anomaly has surgical importance, for it cannot be recognized before operation. Persons afflicted usually have a status thymicolymphaticus with accompanying susceptibility to surgical shock or infection. There is a potential reduced production of epinephrine, with always the possibility of an acute epinephrine insufficiency following a nephrectomy. Kidneys to be removed should be carefully scrutinized for this anomaly during and immediately after operation, because knowledge of the defect might save the removal of the suprarenal gland during nephrectomy or, if it is inevitable (as it was in the case reported here), the epinephrine insufficiency which might develop would be anticipated.—Author's Abst..

**Action of adrenaline on the isolated heart.** Chio, M., Arch. di farmacol. sper. 45: 44. 1928. Abst., Chem. Absts. 22: 3324.

The frog heart was isolated and left *in situ* with a glass canula penetrating into the ventricle through the abdominal cavity, the veins being ligated in such a way as to avoid injury to the chest. Ringer's solution was perfused continuously at a diastolic pressure of about 5 cm. H<sub>2</sub>O, and systolic pressure of about 13 cm. H<sub>2</sub>O. Under the influence of adrenalin in concentrations of 1:100,000 to 1:10,000,000 the same variations in the work of the heart resulted as were obtained by very light circular compressions on the chest and on the auricles.

**A study of the adrenal cortex in the mouse and its relation to the gonads.** Deanesly, R., Proc. Roy. Soc. s. B. 103: 523. 1928.

The two adrenals of the animals were always histologically similar. In the young female about two-thirds of the adrenal cortex may be occupied by a dark staining or X zone. When the female becomes older, this X zone disappears and the cortex becomes similar to that of the male. At three weeks of age the adrenals of both sexes are similar. The inner zone of the cortex disappears in the adrenal gland of the male, but in that of the female it grows rapidly, so that at five weeks it may occupy about half of the cortex. The author from the material at hand cannot say at what age the X zone begins to break down, but in some cases it may be intact in a 12 weeks' old mouse. This degenerative process is slow. The changes observed in the cortex showed no relationship to the oestrus cycle. Pregnancy causes a rapid and complete degeneration of the X zone. In the males which were castrated, the adrenals increased in size, but there was no increase in size of the medulla. These mice develop an X zone which is similar to the X zone of the adrenal of the female mice. Ovariectomy, however, does not influence the adrenal gland of the female. Adrenalectomy increased the length of the oestrus cycle by one day.—E. L.

**Hypotension following adrenin in tabetics (Action hypotensive de l'adrénaline chez les tabétiques).** Dumas, A., R. Froment and Miss Mercier, Compt. rend. Soc. de biol. 99: 76. 1928.

In tabetics, subcutaneous injection of adrenin is followed by a prolonged fall in blood pressure.—J. C. D.

**Addison's disease in the negro.** Evans, L. S., Am. J. M. Sc. 176: 499. 1928.

This author believes that Addison's disease is more prevalent among negroes than the literature reveals because of the prevalence of tuberculosis among them. A survey of the Index Medicus listed only one case. Three cases are reported with complete case histories. In one of the cases, the diagnosis was confirmed by autopsy, but the evidence for diagnosis of Addison's disease in the other two cases was good.—E. L.

**Carcinoma of the pancreas: clinical observations.** Friedenwald, J. and T. S. Cullen, Am. J. M. Sc. 176: 31. 1928.

This study deals with 37 cases, of which 29 were confirmed by autopsy. Nearly all of the cases were in individuals between 40 and 70 years of age. The initial symptoms were a mild digestive discomfort after meals. As the disease progressed, pain, nausea, vomiting and cachexia were noted. The stools were usually acholic and pasty. The pancreatic secretion usually showed a diminished activity of the ferments. The liver sometimes becomes enlarged,



this being noted in 17 of the cases. The gall bladder may become distended and palpable as a pear-shaped tumor. (Noted in 23 of the cases.) This involvement of the gall-bladder and liver may be recognized by disturbances of the biliary and hepatic functions. Transient glycosuria was observed in 6 cases. Cancer, however, is rarely the cause of diabetes. Diagnosis of cancer of the pancreas can be made in 50 per cent of the cases. The tumor, which is usually located in the head of the pancreas, may be palpated in some instances. The duration of the disease in these 37 cases was only 8 months. Operative treatment has proven unsatisfactory because the malignant growth usually has its seat in the head of the pancreas, which is the most unfavorable for resection.

—E. L.

**A case showing underweight unrelieved by fattening with the use of insulin**  
(*Cas de maigreur résistant au traitement d'engraissement par l'insuline*).  
Fonseca, F., *Compt. rend. Soc. de biol.* 98: 1590. 1928.

The patient showed asthenia, vagotonia, muscular pains, increased sensibility to insulin, and a hypoglycemic curve after a glucose meal. The picture is due possibly to adrenal hypofunction, hence the failure to respond to insulin treatment.—J. C. D.

**Observations upon adrenalectomized cats treated with the cortical hormone.**  
Hartman, F. A., F. R. Griffith, Jr. and W. E. Hartman, *Am. J. Physiol.* 86: 360. 1928.

A condition simulating chronic adrenal insufficiency was produced by the daily injection of extracts of the adrenal cortex into 108 completely adrenalectomized cats. The symptoms were those of acute insufficiency except that they tend in general to develop more gradually. In a majority of the animals treated with extract, the metabolism remained within normal limits for periods ranging from 7 to 29 days after removal of the second adrenal. The animal never gained weight and usually lost long before the onset of terminal symptoms. These animals were less resistant to cold and infections. They fatigued more readily than did normals. Overeating caused the blood urea to rise, and brought on symptoms of adrenal insufficiency. In a few instances the skin changed from pink to gray in color. A chocolate-brown subcutaneous fat was found in a cat which survived 300 days. Thyroidectomy and gonadectomy (5 cases) apparently did not modify the survival period of treated adrenalectomized cats.—R. G. H.

**Functional insufficiency of the suprarenal glands.** Mills, C. A., *Arch. Int. Med.* 42: 390. 1928.

A functional disturbance common in the tropics and Orient is described and illustrated by a report of 40 cases. The principal features of the disturbance are: (a) hypermotility of the gastro-intestinal tract, with frequent occurrence of cardiospasm, pylorospasm and ileocecal or sigmoid spasm; (b) these motor disturbances may lead to nausea, vomiting, epigastric or abdominal pain and either diarrhea or constipation. The pain and other symptoms may simulate chronic appendicitis, peptic ulcer or tuberculous enteritis; and (c) there is also usually present gastric hypochlorhydria or achlorhydria, marked vascular hypotension and moderate anemia. Hypoglycemia with high tolerance for dextrose, weakness and loss in weight, urticaria, edema, pigmentation of the skin and menorrhagia also were observed. Foreigners are more susceptible to this trouble than natives. It seems to be definitely related to the coincidental peaks of humidity and heat, when cooling of the body becomes difficult. In some of the foreigners, the onset of trouble was clearly associated with their

first contact with the intense humid heat, while in many others the onset followed their first summer in China. Relief of the symptoms by the oral administration of epinephrine was usually immediate and complete. Autopsy in one case did not show anything to account for the severe condition except changes in the suprarenals characteristic of those seen in animals subjected to moist heat. The conclusion seems justified that suprarenal insufficiency is responsible for the clinical picture presented, and that this represents a distinct disease entity just as truly as does hypothyroidism or hyperthyroidism. Subsidiary conclusions to be drawn from this report are: (a) diagnosis of tuberculous enteritis, peptic ulcer or chronic appendicitis should be made with due caution, to rule out all purely functional disturbances; (b) as a treatment for spastic constipation, the oral administration of epinephrine seems effective and often curative; and (c) many patients with so-called sprue are possibly suffering from suprarenal insufficiency.—Author's Summary.

**The lactic acid in muscles of decapsulated rats (*L'acide lactique musculaire des rats surrénaloprives*).** Mazzocco, P., *Compt. rend. Soc. de biol.* 99: 174. 1928.

Rats were tested ten, thirty, and sixty days after adrenalectomy. The lactic acid was taken immediately after a minute of tetanization and after intervals of rest following tetanization. The controls showed less lactic acid as well as a more rapid disappearance of it from the muscle than did the adrenalectomized animals.—J. C. D.

**Carcinoma of the suprarenal.** Neligan, G. E., *Proc. Roy. Soc. Med. (Sec. Dis. Child.)*, 21: 1321. 1928.

The case described was that of a girl 5 years old. For six months the mother had noticed an increase in size of the child's abdomen. The child complained of occasional abdominal pain. She also appeared to be maturing rather rapidly. On examination, the child appeared several years old than her age. The distension of the abdomen and the left side appeared to be due to a hard, fixed, smooth tumor, which was dull on percussion and did not move with respiration. The pubic hair was well developed. Operation revealed a tumor fixed to the posterior abdominal wall and to the upper pole of the left kidney. The tumor and the left kidney were excised and the child made an uninterrupted recovery. The pathological report was that of solid polygonal and giant celled carcinoma of suprarenal.—I. B.

**Addison's disease.** Phear, A. G., *Proc. Roy. Soc. Med. (Clinical Sec.)* 21: 1167. 1928.

The case described occurred in a woman of 25, who was admitted to the hospital in November, 1927. There occurred marked pigmentation, which was generalized except for the scalp and mucous membrane. It was most pronounced on the face, back of neck, arm and nipples. The blood pressure was low. There were no evidences of alimentary tract or pulmonary disorder. In February, 1928, the patient was again under observation. Pigmentation was more marked, the color being a deep brown; fingers and knuckles were blackish, and the lines of palms of the hands mapped out by deep pigment. The mucous membrane of the cheeks was now involved, and there were a few almost black spots on the arms and legs. The patient had recently suffered from attacks of hiccoughs, which were very severe and lasted from 10 to 15 minutes. There was also marked loss of vigor, though she had worked as a typist. The blood pressure was lower than previously. Treatment did not relieve the symptoms.—I. B.

The influence of blood from the adrenal vein of rabbits before and after a stimulation of the splanchnic nerve on the isolated intestine (*Zur Frage des Einflusses von Blut aus der Nebennierenvene des Kaninchens vor und nach einer Reizung der N. splanchnici auf den isolierten*). Ptschelina, Alexandra, *Ach. f. d. ges. Physiol.* **220**: 371. 1928.

Blood contains other substances besides adrenine which have the typical adrenine action on the isolated intestine; following adrenal extirpation, blood taken from other veins has the typical adrenine action of the preparation. Hence the isolated intestine cannot be used as a specific method for showing presence of adrenine in blood.—A. T. C.

**Acid-base equilibrium after bilateral nephrectomy.** Swingle, W. W., *Am. J. Physiol.* **86**: 450. 1928.

Bilaterally nephrectomized dogs do not develop intoxication. In some cases a slight fall in alkali reserve may occur, but the change is in striking contrast to the acidosis which follows adrenal removal. Blood sugar increases slightly after total kidney removal, but falls markedly after adrenal extirpation. High figures for inorganic phosphate, sulphate and urea are found after nephrectomy and adrenalectomy. Blood chlorides fall as sulphate and phosphate rise following nephrectomy. The suggestion is made that the acid intoxication of adrenal insufficiency and probably also of uremia is extrarenal in origin, since it is not present in nephrectomized dogs with total suppression of kidney function.—Author's Summary.

**Studies on suprarenal insufficiency.** 1. The effect of suprarenal insufficiency on reproduction and the oestrus cycle in the albino rat. Wyman, L. C., *Am. J. Physiol.* **86**: 528. 1928.

Of twenty-eight doubly suprarenalectomized rats which were exposed to males, fifteen became pregnant and thirteen had normal litters. At autopsy eleven of these rats were found to have gross accessory cortical tissue. Of the thirteen that did not become pregnant six died of suprarenal insufficiency and three of the seven that survived had gross accessory cortical tissue. Single suprarenalectomy or a blank operation did not disturb the regular occurrence of oestrus cycles. Forty-one female rats of breeding age were studied by the vaginal smear method both before and after double suprarenalectomy. In sixteen of twenty-three rats which died of acute or subacute suprarenal insufficiency there was practically complete inhibition of oestrus after operation. In six of eight rats which died of chronic suprarenal insufficiency there was marked prolongation of the dioestrus pauses after operation. In eight of ten rats which survived until they were killed for autopsy from three to four and a half months after operation there was no serious disturbance in the occurrence of oestrus cycles. Seven of this group of ten were found to have gross accessory cortical tissue. The use of a vital dye selective for the corpora lutea in four cases showed that persistent dioestrus after suprarenalectomy as shown by the vaginal smear is due to suspension of ovulation. Weight changes after suprarenalectomy were correlated with the clinical findings and the oestrus history, indicating a disturbance of metabolism. The body temperature changes that occurred after suprarenalectomy were not sufficient to account for the disturbance in the oestrus cycles. It is concluded that suprarenal insufficiency in rats results in partial or complete inhibition of oestrus, the degree of disturbance of ovarian function being correlated with the severity of the insufficiency. It is suggested that the relationship between the functioning of the suprarenal glands and the gonads is not direct, but that it is indirect through the mediation of other factors, probably metabolic in nature.—R. G. H.

**The influence of adrenalin on the human spleen and blood picture.** Yang, C. S., *Chinese J. Physiol.* 2: 163. 1928.

Subcutaneous injection of adrenalin was found to markedly decrease the size of the spleen in patients with splenic enlargement. Simultaneously the hemoglobin, red blood cells and white blood cells definitely increased the splenic contraction. A smaller increase was found to occur in the blood cellular elements of normal persons. On the contrary, in splenectomized patients no increase of the red cells or hemoglobin was caused by adrenalin injection, but there was an increase of white cells, though not as marked as with normal or splenomegalic persons. The author assumes that this increase of cellular elements is produced by the mechanical squeezing of the contracted spleen following the adrenalin injection, thus confirming the work of Barcroft that the spleen acts as a reservoir of blood.—L. G. Kilborn.

**Headache.** Drury, D. W., *New England J. Med.* 199: 167. 1928.

The author includes, in his general consideration of the causes of headache, a series of cases of endocrine disorders in which headache was the presenting symptom. These involved disturbances of the pituitary, thyroid, or gonads.

—J. C. D.

**The vegetative nervous system, hypercholesteremia and arteriosclerosis (Vegetative Nervensystem, Hypercholesterinämie und Arteriosklerose in Ihren Beziehungen zu Einander).** Glaser, F., *Klin. Wchnschr.* 6: 2377. 1927.

The author quotes numerous references in the literature to show a relationship between the autonomic nervous system and the blood lipoids (cholesterol and lecithin). He further reports eight cases in which he observed a rise in the blood cholesterol following sympathetic stimulation by the subcutaneous injection of 1 mg. adrenalin. He believes there is a relationship between the activity of the vegetative nervous system and hypercholesterolemia and the development of arteriosclerosis.—S. Shapiro.

**A hormone mechanism for gall-bladder contraction and evacuation.** Ivy, A. C. and E. Oldberg, *Am. J. Physiol.* 86: 599. 1928.

The injection of the following substances into the duodenum of the dog caused the gall-bladder to contract with the animal under light barbital-ether anesthesia: 15 to 40 cc. of N/10 HCl, 30 cc. of butter, digested egg yolk, cream and olive oil, 0.5 per cent butyric acid and 5 per cent soap solution. Undigested olive oil, egg-yolk and cream were ineffectual. Spontaneous rhythmic contractions of the gall-bladder were observed to occur from 2 to 4 times a minute. A small dose of "cholecystakinin" would usually increase their amplitude to as much as 3 cm. of bile pressure; a large dose would usually cause them to disappear at the height of the contraction, but they would reappear some time during the period of relaxation. If they were not present prior to the injection, they would frequently appear during the latter part of the period of relaxation. We have observed the hepatic ducts to be injected with lipoidol during the contraction of the gall-bladder, the injection of the ducts being due, we believe, to increased (abnormal?) tone of the duodenum or sphincter of Oddi.—Authors' Abst.

**Results of castration in turkeys (Influence de la castration chez le Dindon).** Athias, M., *Compt. rend. Soc. de biol.* 98: 1606. 1928.

The usual loss of male characters in structure, voice, and instinct follow castration.—J. C. D.

**The development and morphology of the gonads of the mouse. Part III. The growth of the follicles.** Brambell, F. W. R., Proc. Roy. Soc. S. B. 103: 258. 1928.

In this microscopic study of the ovary of the mouse, the author has found the following: In any one ovary, oocytes at all stages between the smallest ( $13\ \mu$ ) to the full grown ( $70\ \mu$  in diameter) may be found. At the time the oocyte is mature, the follicle is  $125\ \mu$  in diameter. The growth of the follicle and oocyte are correlated up to this point, but afterwards the follicle increases in size independently of the oocyte. The subsequent changes in the oocyte do not increase the size, but the follicle may grow to  $550\ \mu$  in diameter. Ovulation in the mouse takes place during late pro-oestrus or very early oestrus. The average number of follicles maturing at the oestral period was 9.3.—E. L.

**The regulation of the contracting uterus by hormones (Recherches expérimentales sur la régulation hormonale de la contractilité utérine).** Brouha, L. and H Simonnet, Arch. Internal. de physiol. 29: 94. 1927.

From the experimental results there are two distinct actions of the follicular liquid. The specific female sex hormone which regulates the development of the uterus is called *folliculine*. The one which caused rhythmic contraction of the uterus in vitro is called the oxytocic hormone. The effect of oxytocic hormone is similar to that of pituitrin.—E. L.

**Physiology of the corpus luteum. I. The effect of very early ablation of the corpus luteum upon embryos and uterus.** Corner, G. W., Am. J. Physiol. 86: 74. 1928.

This paper reports experiments designed to test again Fränkel's results on the indispensability of corpora lutea for the maintenance of pregnancy in the rabbit, and Bouin and Ancel's results on the necessity of these glands for the pre-gestational proliferation of the endometrium. Three sets of experiments resulted as follows. (1) After ablation of both ovaries no ova survive the early blastocyst stage and the endometrium fails to proliferate as in early pregnancy. (2) After removal of one ovary and half-resection of the other, or after resection of both ovaries, with as little as one-fourth of the ovarian tissue remaining, so long as this contains one or more corpora lutea, the embryos develop normally in a normal proliferating uterus. (3) After removal of all of the corpora lutea with survival of one-sixth to one-half of the ovarian substance, the results are similar to those following double oöphorectomy, though with some unexplained irregularities. The experiments make it seem likely that in the so-called "premenstrual" stage the human endometrium develops likewise under the influence of the corpus luteum.—Carl Hartman.

**Note on the ovarian hormone: Influence of the corpus luteum on the oestrous cycle (A propos des hormones ovariennes: Influence du corps jaune sur le cycle oestrien).** Cotte, G. and G. Pallot, Compt. rend. Soc. de biol. 99: 69. 1928.

Human corpora lutea were grafted into two groups of female rats, one group of which was spayed and the other normal. If the corpora had been removed during the latter half of the menstrual cycle, they had an inhibitory action on the cycle in the rats. If removed from the human earlier than the 14th day after menstruation began, they had a double action. In the spayed rats there were one or two oestrus cycles and in the normals prolonged and accelerated cycles. This stimulating effect was then followed by an inhibitory one, as with the older corpora.—J. C. D.

**The relation of insulin to ovulation** (*L'insuline et ses rapports avec l'ovulation*).  
Cotte, G. and G. Pallot, *Compt. rend. Soc. de biol.* **99**: 74. 1928.

Injection of therapeutic doses of insulin into rats is followed by cessation of the oestrus during the treatment. The ovaries show no ripe follicles, atresia of numerous follicles, and apparently destruction of the ovum in the primordial follicle.—J. C. D.

**Irradiation of ovaries and hypophysis in disturbances of menstruation.** Drips, Della G. and Frances A. Ford, *J. A. M. A.* **91**: 1358. 1928. *Abst. A. M. A.*

The continued study of a group of cases of primary oligomenorrhea and amenorrhea and of menorrhagia and metrorrhagia has further convinced the authors of the existence of an essential ovarian hypoactivity in both conditions. The occurrence of spontaneous remissions and the variable results with all forms of treatment add difficulty to the evaluation of a new method. Low dosage irradiation of the ovaries or hypophysis offers an additional therapeutic measure in intractable cases. The low dosage irradiation has given a comparatively high percentage of favorable results in view of the severity of symptoms in the cases in which it has been used, and regulation, when attained, has continued over a relatively long period. In experimental studies, which are still incomplete, an attempt was made to gauge the amounts of Roentgen rays for application to the ovaries of white rats which might be comparable to low dosage irradiation in the human being. Certain immediate variations in the estrual cycle without disturbance of late regularity were obtained. In most instances fertility was not affected. The second and third generations of the irradiated rats were normal. It was not possible to demonstrate precocious sexual development of immature rats by irradiation of the hypophysis with varying amount of Roentgen rays.

**On the relation between the number of corpora lutea in the rabbit and the degree of preparation in the uterus for implantation** (*Sur les relations entre le nombre de corps jaunes et le degré de préparation de l'utérus à la nidation de l'oeuf chez la Lapine*). Joublot, J., *Compt. rend. Soc. de biol.* **98**: 1541. 1928.

The changes in the uterus in preparation for implantation depend on the presence of corpora lutea. If the lutean material is reduced below a minimum (between one and two corpora), the changes in the uterus are not as intense as normal, though reaching their maximum at the normal time. More lutean material than the minimum does not intensify the reaction in the uterus beyond the normal.—J. C. D.

**Female (Sexual) Hormone: Menformon and standardized ovarian preparations.**  
Laqueur, E. and S. E. De Jongh, *J. A. M. A.* **91**: 1169. 1928.

In answer to the demand for exactly standardized ovarian hormone, Ernst Laqueur and S. E. De Jongh, Amsterdam (*Journal A. M. A.*, Oct. 20, 1928), recommended the standardized, limpid, watery solution of the Menformon, whose preparation and development is essentially based on the American discoveries. Menformon has been in clinical use for two years and a half and for two years it has been available commercially in Europe. The degree of purity obtained in preparations of Menformon is already considerable (0.0008 mg. per mouse unit in the best preparations). Other points of importance are its solubility in water and its power to dialyze through membranes and to resist various agents. On the biologic side, the most remarkable facts are that Menformon is able to produce true estrus in castrated immature or senile rodents; to induce

growth of the juvenile uterus in all species of mammals observed up to this moment, and to cause development of the secretory as well as that of the external parts of the mammae not only in females, but also in males, whether these are castrated or normal. Further, Menformon specifically increases metabolism only in female, and not in male castrates; it has an antimasculine effect in decreasing the velocity of development of the sexual organs in young male animals and in reducing the size of these organs in adult males. Its occurrence in the blood and urine opens up the possibility of computing a hormone balance for various individuals. Another interesting feature is its presence in small amounts in the testes and in urine of normal men. In view of its perfect harmlessness even when large doses are injected intravenously (up to 2,000 mouse units in dogs), we felt justified in advising the use of Menformon in clinical practice; it may be administered subcutaneously as often as required, as clinical experience has shown that this method of administration is devoid of danger.

**The influence of follicular liquid from a case of nymphomania on the vaginal smear in the rat (*Influence du liquid folliculaire provenant d'une nymphomane sur la réaction vaginale du rat*).** Cotte, G. and G. Pallot, *Compt. rend. Soc. de biol.* 98: 1336. 1928.

The liquid, when injected into a spayed rat, produced typical oestrous changes in the vaginal smear. Blood taken from this same case during the premenstrual period also gave similar changes when injected.—J. C. D.

**Reactivation of the senile ovary and the whole female organism by hormonal procedure (*Reaktivierung des senilen Ovars und des weiblichen Gesamtorganismus auf hormonalem Wege*).** Steinach, E., H. Kun and W. Hohlweg, *Arch. f. d. ges. Physiol.* 219: 325. 1928.

Experiments were made with senile female rats 2 to 5 months after cessation of oestral cycles, when typical appearances of senility were present, including loss of hair, partial baldness, bowed attitude, somnolence, and anemia. Following the administration of the active hormonal preparation, there was a recommencement of normal estrus, regeneration of the ovaries (microscopically detectable by the re-occurrence of large ripe follicles and fresh corpora lutea, and functionally shown by the occurrence of spontaneous cycles after cessation of injection), regeneration of the uterus, growth of hair and disappearance of baldness, improved circulation, strengthening of body musculature and increase of nerve irritability (illustrated by the regaining of the former elasticity of force of movement), and finally increase of metabolism, with increased appetite and gain of weight. The psychical re-awakening corresponded.—A. T. C.

**Effect of high temperature on the gonads of frog larvae.** Witschi, E., *Proc. Soc. Exper. Biol. & Med.* 25: 720. 1928.

Frog larvae which had been raised under nearly optimal conditions up to the 7th week were subjected after the 34th day to the maximal temperature that can be endured permanently, 32° C. The gonads of both males and females grew much slower than those of normal controls. However, the spermatogonia of the testis were of about normal size and the seminiferous tubules differentiated in a typical way. The reactions of the ovaries are more complex and more important. At the time when the temperature was raised the ovaries contained large numbers of young ovocytes in the synapsis stage. Two weeks later this type of germ cells had completely disappeared. The ovogonia

are still present and the deeper layers of the cortex contained large auxocytes. The latter, however, were in degeneration. Their nucleoli were extremely large and basophilic and the ovoplasm contained coarse granules. Immediately after the differentiation of further ovocytes had come to an end, the medullary part of the ovarian sac (rete ovarii) transformed into a typical rete testis, vasa efferentia and seminiferous tubules. At first the latter completely lacked germ cells. However, sooner or later the ovogonia migrated from the cortex to the medulla, and after having entered the seminiferous tubules transformed into spermatogonia. Thus the experiment led to the total reversal of sex of the females. The normal controls consisted of 100 females and 96 males. The experimental group contained no typical females after the second week of rise in temperature; but between the 15th and 33rd day 53 females in different stages of sex transformation and 62 typical males were preserved.

—Author's Abst.

**A hormone of heart movement. X. Warm blood experiments with the heart hormone preparation (Ueber ein Hormon der Herzbewegung. X. Warmblütersversuche mit dem Herzhormonpräparat).** Haberlandt, L., Arch. f. d. ges. Physiol. 220: 203. 1928.

Results similar to those given by frog hearts were obtained with rabbit hearts.—A. T. C.

**A case of diabetes insipidus caused by hypernephroma metastasis in the midbrain.** Elmer, A. M., J. Kedzierski and M. Scheps, Wien. klin. Wchnschr. 41: 591. 1928.

A case of diabetes insipidus which came to autopsy and revealed a hypernephroma metastasis in the midbrain, with little or no involvement of the pituitary gland, is reported. The urinary output was about 5 liters daily, and the urine contained 0.1 per cent of sugar. The blood sugar was 230 mgm. On a low carbohydrate diet, the blood sugar fell to 110 mgm. Protein injections and various pituitrin preparations were without effect on the polyuria, and insulin given with pituitrin increased the urine volume. The polyuria and glycosuria are explained as the result of the destruction of water, salt, and sugar metabolism regulating centers in the midbrain.—R. B. Gibson.

**Case of dyspituitarism.** Worster-Drought, C. and B. W. C. Archer, Proc. Roy. Soc. Med. (Neurol. Sec.) 21: 1513. 1928.

The patient was a male of 15 who was of unusual size for his age and presented excessive obesity, difficulty in walking, attacks of vomiting and mental backwardness as the outstanding clinical features. He did not walk until nearly three years old, and between three and four he began to grow in stature rapidly and became much more obese than the average child of his age. At that time it was noticed that he was backward mentally. He was entered at school at the age of 5, but made no progress and has never learned to read or write, though he has shown some interest in mechanical things. Attacks of vomiting at night were frequent, but there were no headaches. Sight and hearing were good. There appeared to be no significant points in the family history except that the father's appearance suggested acromegaly. Examination of the patient revealed the height of 73 inches, with typical physical evidences suggestive of dystrophia adiposo-genitalis.—I. B.



**Effect of ligature of pancreatic ducts on the regulation of the glycogen titer.** Caccuri, S., *Boll. d. Soc. ital. di biol. Sper.* **2**: 918. 1927. *Abst., Chem. Absts.* **22**: 3440.

The pancreatic ducts of 4 dogs were ligated and every 15 days dextrose solution was injected by way of the jugular vein and the free and combined sugar was determined. Two dogs died, but in the remaining after 75 to 90 days it was found that after injection of sugar the combined sugar increased, while free sugar diminished; i. e., similar results as would result from insulin injection. Apparently a tolerance for sugar is gradually acquired. The pancreas was found atrophied and changed almost wholly to connective tissue.

**Action of insulin on the capillary circulation.** Cuenca, B. S., *Rev. med. de Barcelona*, **9**: 398. 1928. *Abst., Physiol. Absts.* **13**: 295.

Experiments are detailed to show that insulin has a vaso-dilator action on small capillaries. The effect of insulin on producing a more rapid passage of glucose into muscle is thus due to its vaso-dilator action on the muscle capillaries.

**Changes in the blood sugar of normal subjects following treatment of the pancreas with x-ray (Modifications de la glycémie chez des sujets normaux par l'irradiation du pancréas).**

**Effect of irradiating the pancreas on the glycemia and glycosurea in diabetics (Action de l'irradiation du pancréas sur la glycémie et la glycosurie des diabétiques).** Fonseca, F. and C. Trínaco, *Compt. rend, Soc. de biol.* **98**: 1591-1592; 1593-1594. 1928.

In the normals, one-half of an erythematous dose produced a reduction in blood sugar and a change in the curve following glucose ingestion, probably due to an increased output of insulin. In three diabetics, the glycosurea and hyperglycemia were reduced for several days.—J. C. D.

**Ocular complications of diabetes.** Gifford, S. R., *M. Clin. North America*, **12**: 423. 1928.

True cataract may occur, but is rare, while senile cataract occurring in the diabetic is common and does not differ from cataract in the non-diabetic. With a little pre-operative care to reduce the urinary sugar to the minimum, operation in these cases is not attended by any great risk. Cataract and rapid changes in refraction occurring in diabetes are probably the result of changes in the osmotic pressure of the blood. Retinitis occurs chiefly in diabetics past the age of 50, often with renal or vascular complications, but also without any signs of these. It may be the only sign of an abnormal condition of the vessels in these patients. The prognosis for life and vision is relatively good in diabetic retinitis, in contrast to that of albuminuric retinitis.—I. B.

**Simultaneous stimulation of the external and internal secretions of the pancreas (Excitation simultanée de la sécrétion externe et de la sécrétion interne du pancréas).** Gley, E. and R. Hazard, *Compt. rend, Soc. de biol.* **99**: 16. 1928.

The injection of hydrochloric acid into the duodenum stimulates the external secretion of the pancreas. It, likewise, increases the production of insulin, as is shown here by studies on the blood sugar changes in dogs.—J. C. D.

**The effect of insulin upon polyuria in diabetes insipidus; the combined effect of insulin and pituitrin upon water metabolism.** Klein, O. and H. Holzer, *Deutsche Arch. f. klin. Med.* 156: 111. 1928. *Abst., Chem. Absts.* 22: 3458.

The attempt has been made to employ for differential diagnosis the effect of insulin upon the diuresis of diabetes insipidus; but there is not sufficient justification, since the hypo- and hyperchloremic forms are not so easily distinguished by their reaction to insulin alone. In those cases where insulin alone was observed to be without diuretic effect, the effect became manifest when pituitrin was injected with the insulin. The antidiuretic effect of insulin is then an intensification of the effect of the pituitrin. In a case of syphilis, where the hypophysis was seriously affected, the antidiuretic effect was entirely lacking when insulin alone was administered; in similar cases which did not involve the hypophysis the effect was definite. In a case of lesion of the hypophysis the diuretic effect was observed only when insulin and pituitrin were injected together. The results were influenced quantitatively by the size of the dose, and by the amounts of water and of carbohydrate consumed during the experiment. The use of insulin produces perfectly regular results where carbohydrate metabolism and the water-binding ability of the organism are seriously disturbed. The effect of the insulin is upon the carbohydrate metabolism, and only indirectly upon the diuresis.

**Synthalin in diabetes mellitus.** Lyon, D. M., *Edinburgh M. J.* 35: 357. 1928.

Fourteen diabetics were used and tested either for the ability of synthalin to clear up glycosuria without insulin or its power to maintain a satisfactory carbohydrate balance after insulin had been used. Synthalin had a distinctly favorable action under both of these conditions.—J. C. D.

**Prolonged insulin hypoglycemia without symptoms.** Maddock, S. J. and H. C. Trimble, *J. A. M. A.* 91: 616. 1928. *Abst., A. M. A.*

In connection with some experiments on the corpuscle-plasma distribution as related to insulin shock, the authors were particularly impressed by the length of time that hypoglycemia can exist before symptoms appear. Experimental evidence shows that, following insulin administration, the blood sugar of diabetic patients and depancreatized dogs may remain at levels of 50 mgm. per cent or below for from one to six hours without symptoms. Such periods may or may not be followed by hyperglycemic reactions. They believe that this phenomenon, whose dangers are evident, is probably frequent in occurrence; that it usually is unrecognized, and that it may account for the difficulty so often encountered in regulating the administration of insulin. It is tempting to the authors to reason by analogy that if continued high blood sugar overstrains the pancreas, continued low blood sugar may over rest it.

**Experiments on fats and lipoids in blood. IV. The partition of fats and lipoids in the blood of dogs with pancreatogenic diabetes after insulin injection** (*Untersuchungen über Fette und Lipoids im Blute. IV. Ueber die Verteilung der Fette und Lipoide im Blute nach der Insulininjektion bei Hunden mit pankreatogenem Diabetes*). Morimoto, M., *Arch. f. d. ges. Physiol.* 219: 733. 1928.

The fat and lipid content of blood decreases following total extirpation of the pancreas. A marked increase takes place in such animals following injection of insulin. The corpuscular content is not changed, nor is the ratio of cholesterol to total lipid, by either pancreatectomy or insulin injection; the changes take place in the plasma.—A. T. C.

**Diabetes mellitus and pregnancy.** Walker, A., *Proc. Roy. Soc. Med. (Sec. Obs. & Gynec.)* 21: 377. 1928.

This paper gives the results of a thorough search of the available records for cases of diabetes mellitus and pregnancy, with a view to showing that since the use of insulin one may be justified in disregarding the advice given in most textbooks that it is extremely dangerous for a diabetic woman to become pregnant, and that, if unfortunately she does, pregnancy should be terminated. From the data collected it appears that the administration of insulin has entirely altered the outlook for the better in cases of pregnancy complicated with diabetes, as it has done in diabetes generally. Although diabetes is itself a very serious disease, and must be regarded as a serious complication of pregnancy, if the patient is treated with insulin and placed on a proper diet there seems to be no ground for terminating the pregnancy, and there is no reason why she should not give birth to a live child. There appears to be no special incidence of puerperium complications. Pregnancy does not appear to have any ill effects on the diabetic condition. Apparently in one case insulin has been the means of curing sterility.—I. B.

**The value of acterol (irradiated ergosterol) in the treatment of thyroparathyroidectomized dogs.** Brougher, J. C., *Am. J. Physiol.* 86: 538. 1928.

"Acterol" in 0.4 cc. dosage, when given along with milk to twelve dogs from the day of operation, prevented the development of violent tetany. Animals which did not retain their milk and thus had no source of calcium showed tetany in spite of the acterol. Recovery was quicker in parathyroidectomized dogs given acterol than cod liver oil. The time for recovery ranges from 15 to 30 days for acterol and 30 to 40 days for cod liver oil. It would seem that a rich supply of vitamin D is efficacious in a large percentage of instances in enabling the body to utilize calcium in the disturbed calcium metabolism found in parathyroid tetany.—R. G. H.

**The effect of thyroxin on the respiratory and nitrogen metabolism of a normal subject following prolonged nitrogen-free diet.** Deuel, H. J., Jr., Irene Sandiford, Kathleen Sandiford and M. Boothby, *J. Biol. Chem.* 76: 407. 1928.

The administration of thyroxin to a normal subject after the depletion of the supply of deposit protein by a nitrogen-free diet for a preliminary period of 30 days did not in any way alter the characteristic effect of the thyroxin on the nitrogenous or respiratory metabolism. However, in spite of an increased urinary nitrogen, which reached a maximum 7 days after the injection of 7 mgm. of thyroxin, there was no change in the creatinine or uric acid elimination, indicating that the endogenous nitrogen metabolism was not augmented. In a later period the maintenance of the respiratory metabolism at an elevated level by the daily administration of small doses of thyroxin only slightly increased the total urinary nitrogen without changing the creatinine or uric acid output.—H. J. Deuel, Jr.

**Endemic goiter in Massachusetts.** Doering, C. R., H. L. Lombard and Fredrika Moore, *New England J. Med.* 199: 143. 1928.

The report is based on the study of 12,270 high school students. The authors conclude that: The partial correlation between the incidence of goiter and the iodine in drinking water shows that the important variable is distance from the ocean. The presence or absence of communicable diseases, enlarged tonsils, adenoids, cervical glands, dental caries, has no apparent effect on goiter

incidence. The mean weight of children with goiter is slightly less than that of non-goitrous children, though this may be apparent rather than real.

—J. C. D.

**A case of post-operative tetany.** Hunter, D., *Proc. Roy. Soc. Med. (Clin. Sect.)* **21**: 1409. 1928.

The case described was that of a woman 44 years old, in whom a sub-total thyroidectomy was performed for the relief of a large endemic goiter. Two weeks after operation symptoms of tetany developed. Four years after operation these disappeared and there were no symptoms for six years, following which they recurred and became more severe than before. Under Collip's parathyroid serum and occasional thyroid opotherapy, relief was complete, but unless treatment was continued the symptoms recurred.—I. B.

**The thyroid and atropine.** Ikonen, M. W. and S. M. Kusnetzowa, *Ztschr. f. d. ges. exper. Med.* **57**: 353. 1928. *Abst., Chem. Absts.* **22**: 3201.

Four parts of serum, one part of an atropine solution and one drop of benzene were mixed and placed in an incubator at 37° for 24 hours. Two drops of the mixture were then placed in one eye of a cat and the pupillary dilation and paralysis observed. The serum of normal rats will neutralize up to a 1:50 solution of atropine. Following thyroidectomy, this power is lost, but returns when thyroid gland is transplanted. Similar results are obtained in patients with thyroid disorder and the method is suggested as a test for thyroid secretion.

**Diabetes and hyperthyroidism.** Joslin, E. P. and F. H. Lahey, *Am. J. M. Sc.* **176**: 1. 1928.

The symptoms found in both these diseases are somewhat similar. In 228 cases of primary hyperthyroidism there were 38.6 per cent with glycosuria. The standard for a diagnosis of diabetes in hyperthyroidism is that the blood sugar should be 0.15 per cent fasting or 0.20 per cent or more after meals, in addition to glycosuria. The authors believe that the hyperthyroid patient is more prone to diabetes than an ordinary individual.—E. L.

**The crisis of exophthalmic goitre.**—Lahey, F. H., *New England J. Med.* **199**: 255. 1928.

This is a general discussion with an outline of the author's methods of treatment. He concludes that: Thyroid crises are by no means rare. The mortality rate in patients permitted to advance into a state of crisis is extremely high. Treatment in this condition is most effectual if vigorously applied when the first signs of the condition appear. The possibility of the onset of a thyroid crisis during treatment must be considered when conservative treatment is adopted in a patient with thyroidism.—J. C. D.

**The familial incidence of exophthalmic goiter.** Morrison, H., *New England J. Med.* **199**: 85. 1928.

This report covers three instances of family goiter, in one of which six cases occurred.—J. C. D.

**The effect of iodine and thyroid feeding on the thyroid gland; an experimental study.** Mösser, W. B., *Surg. Gynec. Obst.* **47**: 168. 1928.

Three groups of dogs were studied. In the first group after a section had been removed for microscopic examination the dogs were given Lugol's solution, 10 minims daily for 6 weeks, and then a second biopsy was done. After

an interval of several months during which no medication was given a third biopsy was done. In the second group, after preliminary biopsy the animals were given thyroid extract in increasing quantities until they exhibited symptoms of hyperthyroidism. A second section was taken. Iodine (Lugol's) was then given for 6 weeks, and then a third biopsy was done. After a rest period of 3 months a fourth section was taken. In the third group the treatment was the same as in the second, with the exception that thyroid extract was continued during the 6 weeks that Lugol's was being given. The results, compared with a series of clinical cases, led to the following conclusions: In the experimental animal iodine stimulates the cells to produce colloid. Colloid retention compresses and flattens the cells of the acini. The same effect occurs from iodine administration in the presence of experimental hyperthyroidism. Prolonged iodine administration to a hyperthyroid animal produces a stage of exhaustion in the gland. The effect of iodine on the normal human gland is similar to that in the dog. The effect of iodine on the hyperplastic toxic goiter is similar to that obtained in the normal gland of the dog. After prolonged administration of iodine (3 to 12 months) to the patient with hyperplastic toxic goiter a stage of exhaustion is noted which is similar to that produced in the dog by prolonged feeding with thyroid extract and iodine. The clinical status of the patient is not proportionate to the histological picture when iodine has been taken for a prolonged period. Plummer's theory of the action of iodine is rejected, and another theory based on exhaustion of the gland by continued iodine stimulation is put forward.—A. T. C.

**Tetany following thyroidectomy.** Pratt, G. P., M. Clin. North America, 12: 319. 1928.

The case described was that of a woman of 31 years, presenting the symptoms of tetany following thyroidectomy for exophthalmic goiter. The symptoms occurred six weeks after operation, and were heralded by cramplike pains in the hands and feet, with severe nose bleed. The author states that 14 per cent of patients operated upon for goiter present symptoms of latent tetany, unrecognized until an infection, a menstrual period, a surgical operation, or some other disturbance sets in. The principle of treatment is the administration of calcium salts and Collip's serum.—I. B.

**Experiments on the action of some iodine compounds of frog larvae (*Untersuchungen über die Wirkung einiger Jodsubstanzen auf Froschlarven*).** Schwaibold, J., Arch. f. d. ges. Physiol. 220: 1: 1928.

Iodine produces in frog tadpoles no definite "thyroxine" metamorphosis, but a positive effect on the development, shown especially by a shortening of the time of actual metamorphosis. The action is specific to iodide, and is not given by chloride or bromide. Milk from cows fed iodide produces only this effect. An iodoprotein, "Iodtropon," also produces the effect of inorganic iodide only, evidently through the breaking off of iodine during gastric digestion. The same result is also obtained when tyrosine and sodium iodide are fed together to tadpoles.—A. T. C.

**On the influence of South-Bavarian goiters on tadpoles and remarks on the technique (*Studien über Südbayerische Kröpfe im Kaulquappenversuch und Bemerkungen zu dessen Methodik*).** Spatz, H., Ztschr. f. Biol. 87: 41. 1927.

The metamorphosis promoting action of human goiter substances on tadpoles was studied. A uniform tadpole material was used. The thyroid glands were obtained at biopsy, dried and pulverized. One dose of the powder was

fed to the tadpoles, which were otherwise, like the controls, fed on calf's liver. The control group was fed a standardized thyroid preparation. On an average the goiter substances showed the same activity in the human body and on the tadpoles. Hypothyroid goiters and goiters of adolescents had no activity. Clinically indifferent goiters accelerated metamorphosis less than the standard thyroid preparation. Hyperthyroid goiters had a strong effect (one exception). Goiters consist of histologically widely different parts; the different parts also vary in their biological action on tadpoles. The biological activity of a goiter is not bound to one histological structure, but is connected sometimes with tissue rich in colloid, sometimes with cellular tissue. On the whole, tissue rich in colloid is more active.—G. T. Cori.

**Hyperthyroidism, without visible or palpable goiter.** Tucker, J., *Am. J. M. Sc.* 176: 504. 1928.

Three cases of hyperthyroidism in which there was no visible or palpable goiter are presented. The soft tissues mask the goiter and the indication for operation is hyperthyroidism and not goiter.—E. L.

**The influence of the thyroid on the higher nerve function of dogs. I. The action of single doses of thyroid on conditioned reflexes under simple experimental conditions** (*Ueber den Einfluss der Schilddrüse auf die höheren Nerven funktionen der Hunde. I. Die Wirkung von Thyreoidea-Einzelgaben auf die bedingten Reflexe bei einfachen Versuchsverhältnissen*). Zawadovsky, B. M. and A. L. Sack, *Arch. f. d. ges. Physiol.* 220: 155. 1928.

For the first few days there is a phase of general suppression of conditioned reflexes, shown especially as a disturbance of, or incomplete suppression of work-differentiation. In the second stage there is a general increase of irritability, shortening of the latency period, and an increase of both the conditioned and unconditioned salivary secretion.—A. T. C.

# ENDOCRINOLOGY

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### HYPERPARATHYROIDISM: TUMOR OF THE PARATHYROID GLANDS ASSOCIATED WITH OSTEITIS FIBROSA\*

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The study of the activity of extracts of endocrine glands is not only giving us a better understanding of diseases formerly familiar such as hyperthyroidism, but is revealing the existence of clinical entities that were unsuspected previously. Experience gained with insulin led to the recognition of a disease that results from spontaneous overactivity of the pancreas, namely hyperinsulinism (20, 28, 32). In a similar manner familiarity with the hormone of the parathyroid glands, for which we are indebted to Hanson (15), Collip (5) and others (3, 17), has revealed another clinical entity, hyperparathyroidism.

The administration of Collip's parathormone (parathyroid extract, Collip) to normal dogs and cats produces an increase of calcium (6) in the blood serum, a tendency for the inorganic phosphorus of the blood serum to decrease (25), an increased excretion of calcium and phosphorus, and thus a negative balance of calcium and phosphorus (12, 13). Decalcification of the skeleton has not been demonstrated in experiments with parathormone, but this would inevitably follow a long continued negative calcium balance. Also, hypotonicity of the musculature might be anticipated since muscular spasticity (tetany) is characteristic of parathyroid deficiency. These conditions are all encountered in clinical hyperparathyroidism. The case reported here is an instance of this disease in which increased parathyroid activity is attributable to the presence of a malignant parathyroid tumor.

Erdheim (8), as early as 1907, commented on the frequency of the occurrence of hypertrophy of the parathyroid glands in cases of osteomalacia, drawing the conclusion that the hypertrophy represented an inadequate attempt at compensation. The alteration of the parathyroid glands, according to Erdheim, was thus a result and not a cause of the disease. Others confirmed Erdheim's observations and Hoffhainz reviewed from reports of pathologists forty-five cases of enlarged parathyroid glands, in

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which were twenty-seven cases of disease of the skeleton (osteitis, fibrosa, seventeen, osteomalacia, eight, and rickets, two).

In 1925 Mandl, of the Hochenegg Clinic in Vienna, proceeded to test Erdheim's theory. If the enlargement of the parathyroid glands was indeed an attempt at compensation, as Erdheim proposed, the engrafting of normal parathyroid tissue should be of benefit in cases of osteitis fibrosa. The successful transplantation of parathyroid glands of man had been reported previously by a number of workers. Mandl removed four parathyroid glands from the moribund victim of an accident and placed them in the abdominal wall of a man aged thirty-eight with osteitis fibrosa. The transplantation was successful but the patient was not benefited; in fact he became worse. Mandl was thus led to consider that hypertrophy of the parathyroid glands might be a cause of osteitis fibrosa and he searched for enlarged glands in this patient with the idea of removing them if they were found. There was no indication of such enlargement from palpation, but on exposure of the thyroid gland surgically a tumor was found on the left side of the trachea behind the gland. This was removed and proved to be a parathyroid adenoma, 25 by 15 by 12 mm., yellowish-brown, and easily distinguishable from the adjacent thyroid gland. Following the operation the patient, who had been unable previously to lift his legs from the bed or bend the knees, regained strength so that he could walk satisfactorily with a cane. Pain in the bones, which had been present, disappeared and although he had not recovered completely two years later, he had gained 16 kgm. in weight and was strikingly improved. The daily excretion of calcium in the urine which before the operation had been approximately 55 mgm. was reduced to 9.6 mgm., and roentgenograms taken four months after the operation disclosed a moderate increase in the density of the bones. The tumor manifested some signs of malignant activity; a few karyokinetic figures were observed, cells and nuclei were inconstant in size and normal parathyroid tissue was not in evidence.

This I believe is the first demonstration of spontaneous hyperparathyroidism although Mandl prudently refrained from drawing any conclusions other than that his experiment had disproved the application of Erdheim's theory to osteitis fibrosa.

Two years later Gold reported an almost identical case in a woman aged fifty-four in von Eiselsberg's clinic. A parathyroid tumor was found in this case also. It was a firm, yellowish-white mass, about the size of the terminal phalanx of a finger and occupied the position of the right inferior parathyroid gland. The patient's symptoms, especially weakness and pain, were appreciably improved after removal of the tumor and in four months she had gained 8 kgm. in weight. The day after operation the patient was sleepy; symptoms of oliguria were present but none of tetanic convulsions. The blood calcium, which had been "about 30 per cent above normal" before operation, returned to normal and the excretion of calcium in the urine which had been "somewhat more than 100 per cent greater



than normal" was reduced for a time to "12 per cent of a normal excretion." Gold, as a result of this experience, advised surgical exploration for tumor of the parathyroid glands in patients with osteitis fibrosa, and Barrenschéen in discussing this case called attention to the similarity between the experiment performed here by nature and the results obtained in experiments on animals with Collip's parathormone.

In the interval between the appearance of the observations of Mandl and those of Gold, DuBois, knowing of the Mandl operation, studied a case of osteitis fibrosa. The patient, a man, was bedridden and had lost 17.5 cm. in height as a sequence of softening of the bones. The blood calcium was abnormally elevated, the electrical excitability of the muscles was reduced and a negative calcium balance was demonstrated. The administration of Collip's parathormone aggravated the symptoms. The patient was sent to Aub, Bauer and Richardson (7) who confirmed the negative calcium balance. At operation a tumor was not found, nevertheless two normal appearing parathyroid glands were removed. Afterward the blood calcium was a little lower and roentgenograms revealed a deposit of calcium in the bones. The patient gained in strength and in four months was able to work in an office eight hours a day. In this instance there was hyperfunction of the parathyroid glands in the absence of any noticeable hypertrophy. The resected glands appeared normal on histologic examination.

The next case to be recognized and treated successfully, the first to be reported as hyperparathyroidism, was that of Barr, Bulger and Dixon. The clinical picture was almost identical with that of the cases of Mandl, Gold and DuBois, the chief features being rarefaction of bones and hypercalcemia (16 mgm. per cent). Complete studies of the metabolism revealed a constantly negative calcium balance with loss of calcium in the urine, which was greater with any increase of calcium in the diet. The blood phosphorus was found to be subnormal (1.4 mgm. per cent). A globular mass could be felt in the neck when the patient swallowed, and operation revealed that this was a parathyroid tumor. Following removal of the tumor the blood calcium fell to below normal and tetany developed, requiring heroic treatment with calcium and parathormone. Retention of a large amount of calcium followed with some gain in muscular strength. Also, a tumor of the maxilla became smaller. This had been diagnosed previously by biopsy as a giant-cell tumor.

The duration of the disability in Mandl's case was five years; it was not stated in Gold's case. DuBois' patient had been bedridden for four years. In the case reported by Barr, Bulger and Dixon, the patient, a woman aged fifty-six, had a complication which is not infrequent in osteomalacia and osteitis fibrosa; namely, renal stone. Some urinary trouble called inflammation of the bladder had been present when she was thirty-eight, but had disappeared. At forty-seven the pain in the bladder and the frequency of urination returned, and from that time the patient was never very well.

Rowntree and Allan of The Mayo Clinic were present when this case was

presented. They recognized a similarity between the symptoms and observations reported and those in a case then under observation in the clinic. As a result this case was diagnosed as hyperparathyroidism.

#### REPORT OF CASE

The patient was a married woman, aged thirty-two years in 1925, born in Canada. Her father had died at the age of sixty-two from carcinoma of the bladder. Her mother, two brothers and a sister were living. There was no record of tuberculosis, migraine or diabetes in near relatives. Menstruation began at the age of fourteen, was always irregular with intervals varying from four to six weeks, and lasting usually eight days; the flow was excessive and associated with moderate pain. Illnesses included diphtheria when she was a child, scarlet fever, and pneumonia with pleuritis at sixteen, influenza at twenty-five followed by pleuritis, and occasional attacks of tonsillitis. The first teeth were all soft and decayed rapidly. Moderate anemia had existed since childhood, also general weakness and nervousness. Her appetite had been capricious since childhood, and overindulgence in sweets and neglect of vegetables, milk and cream resulted. Fresh air and sunshine had been rather avoided. A course of treatment with rest, sunshine and forced feeding had been given in 1921 under the direction of Dr. George Minot. Considerable benefit was derived. In 1922, pain

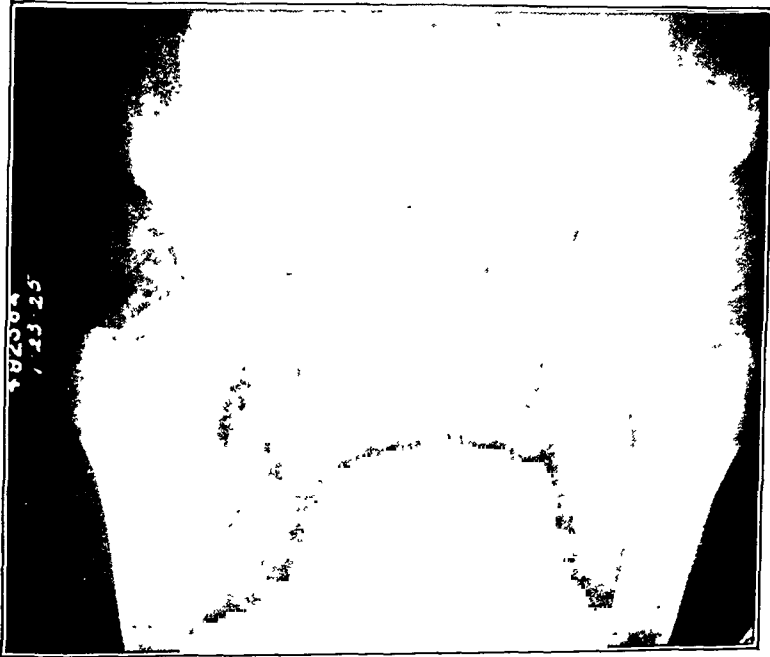


Fig. 1. The pelvis showing decalcification of the bones and cystic areas, but no gross deformity. January 23, 1925.

began in the right hip, associated with stiffness; it later affected the entire body. Standing aggravated the pain in the hip and produced pain in the knees. In 1923, a small lump was noticed in the thyroid gland, and also in that year a small tumor grew from the periosteum of the lower right bicuspid region. This was removed and diagnosed myelosarcoma. In 1924, considerable swelling appeared in the same region; a fairly large area of bone was chiseled away and the floor of the antrum was cauterized. Teeth were removed. Many other teeth had been removed previously on account of decay. Shortly after the operation on the face, an acute attack of appendicitis occurred and appendectomy was performed.

On the patient's admission to The Mayo Clinic, January 13, 1925, she weighed 44.6 kgm. (120 pounds) and was 153 cm. in height. Her complexion was sallow. Her gait was unusual, a swaying, waddling movement, due possibly to an effort to avoid placing much weight on the right leg. In stepping up, the left foot was lifted first and the right dragged after it. All but four teeth were gone, and these were badly decayed; periapical infection was revealed on roent

gen-ray examination. The tonsils were small and not obviously infected. At the lower pole of the right lobe of the thyroid gland was a spherical mass about 3 cm. in diameter, which was believed to be adenoma of the thyroid gland. The lungs were clear; the heart was normal in size. Murmurs which were thought



Fig. 2. The skull showing decalcification and cystic areas. April 15, 1926

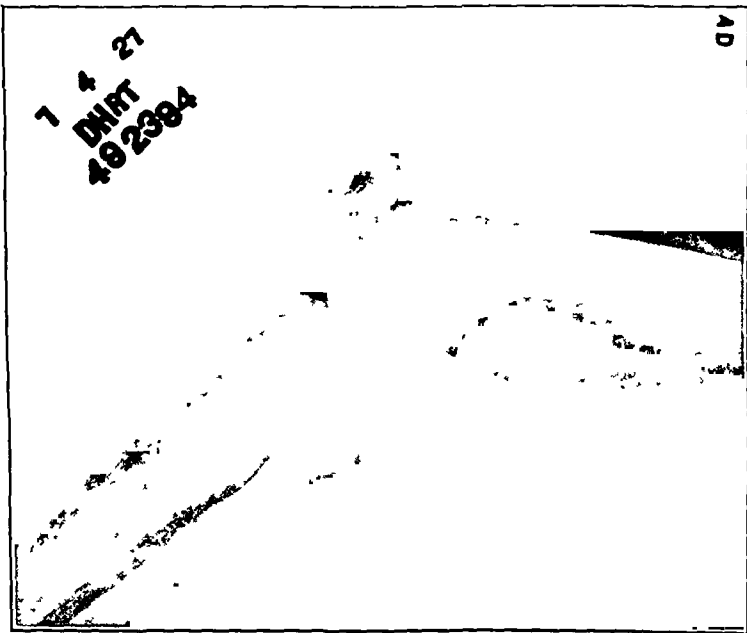


Fig. 3 The right knee. Decalcification and cystic areas at the distal end of the femur are shown July 4, 1927.

to be hemic were heard over the heart. The pulse was fast, usually more than 100. The blood pressure was normal, usually about 120 systolic and 70 diastolic. The abdomen was held rigidly, so that palpation was difficult. At one time it was thought the spleen was palpable, but this was not confirmed at later examinations.

The hymen was not ruptured and the vagina was contracted. The urine was essentially normal. The blood count revealed moderate anemia with a low color index. The fragility of the corpuscles was normal and the leukocytes were normal. Wassermann reactions on the blood and spinal fluid, Nonne reactions and colloidal benzoin reactions were negative. The stools did not contain ova or parasites. Roentgenograms of the pelvic bones showed a rarefaction of the bones, but gross deformity was not present (Fig. 1). The electrocardiogram did not show anything unusual. The basal metabolic rate, January 17, was +12, and February 19, +2. Symptomatic treatment was prescribed and the patient was dismissed from observation.

March 6, 1925, the patient returned to the clinic. The four remaining teeth had been removed, without benefit. Muscular weakness had increased so that she was scarcely able to rise from her bed, and then would have to stand for several minutes before venturing a step with the help of crutches.

April 13, 1926, the pain was affecting all bones and joints; the muscles were not affected. The general weakness had increased. Determinations of the blood calcium and blood phosphorus were made at this time. The calcium was slightly elevated (11.2 and 11.4 mgm. for each 100 cc.). The phosphorus was low (1.4 mgm.). Roentgenograms of the spine, pelvis and skull revealed areas of rarefaction (Fig. 2). The bones of the legs were considered to be normal.

TABLE 1  
Analysis of Bone (After Drying)

Date	Bone	Organic Matter, Per Cent	Calcium, Per Cent	Phosphorus, Per Cent	Magnesium, Per Cent
5-23-27	Crest of ilium	70.0	11.2	8.4	0.31
11-15-28	Femur cortex*	50.0	15.5	6.25	
Average Values**		40.0	22.8	14.6	0.21

\*Average of two determinations, one of more compact bone, the other of more cancellous bone

\*\*Calculated from data given in "A textbook of physiological chemistry" (Hammarsten)

May 15, 1927, the weakness had increased so that the patient was unable to walk even with crutches. The weight had fallen to 36.5 kgm. (80 pounds), and the pains in the bones and joints were more severe. Roentgenograms of the pelvis, femur, spine and ribs revealed rarefaction. A cystic area was noted at the distal end of the right femur (Fig. 3). In places this rarefaction assumed a cystic appearance. After a preliminary period of observation in the hospital a piece of bone was removed from the crest of the ilium for analysis; it contained excessive organic material and was poor in bone salts (Table 1).

TABLE 2  
Nitrogen, Calcium, Phosphorus and Magnesium Balances: Ten-Day Period  
(June 20 to 30, 1927)

	Calcium, gm	Phosphorus, gm	Magnesium, gm	Nitrogen, gm
Output in urine	3.10	5.09	1.12	42.3
Output in stool	4.40	3.27	1.74	
Total output	7.50	8.36	2.86	
Intake*	7.98	10.70	3.71	56.7
Balance	+0.48	+2.34	+0.88	+11.4

\*An equal portion of all food eaten was preserved, dried to constant weight and analyzed

A high vitamin diet and daily treatment with ultraviolet light were instituted. Some time later a ten-day study of metabolism revealed positive balances for calcium, phosphorus, magnesium and nitrogen. This was probably influenced by the treatment (Table 2). Considerable gain in weight and strength and an improvement in the blood count accompanied the positive metabolic balances. There was little if any change in the blood calcium or in the blood phosphorus (Table 3).

November 16, 1928, the patient weighed 44 kgm. (96.5 pounds) and was in a much better general condition than at the previous examination. The height at this visit was 152 cm. She had adhered to the high vitamine D regimen during the interval. There was less pain in most of the bones, but she suffered severely from pain in the bone above the right knee. Roentgenograms again showed the



Fig. 4. The pelvis showing decalcification, cystic areas and deformity (wedge-shaped pelvis). July 4, 1927.

cystic areas of rarefaction above the condyles of the right femur, and general rarefaction as observed previously (Fig. 4). At this time there was also some thickening of the bone of the left cheek and a definite mass was palpable on the anterior aspect of the left maxilla. The blood calcium was moderately elevated as before (12.2 mgm. for each 100 cc.); the blood phosphorus was low (1.9 mgm.). The hemoglobin was 72 per cent and the erythrocytes numbered 4,370,000.

TABLE 3

Weight of Body and Changes in the Blood on High Vitamine D Regimen

Date,* 1927	Weight of Body, kgm.	Hemoglobin (Dare), Per Cent	Erythrocytes for Each Cubic Millimeter	Blood Serum	
				Calcium, mgm Per Cent	Phosphorus, mgm. Per Cent
May 25	36 0	50	3,250,000	10.7	1.8
June 6	38 5	49	3,116,000	13 1	2 0
June 13	41 0	53	3,390,000	11 8	2 3
June 20	42 0	61	3,490,000	12 4	1 9
June 27		60	3,810,000	12 3	3 0
July 5		70	3,740,000	12 3	2 0
July 13	42 5	70	3,890,000	12 2	2 0
July 22	43 5		4,100,000	12 9	2 1
July 29	43 0				
August 15	43 0	55	4,230,000	13 2	1.9

\*Determinations made within the week following the date given.

High vitamine D diet and daily treatment with ultraviolet light instituted June 6.

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The lower end of the right femur was examined by open operation. Nothing unusual was encountered except that the bone was porotic. Microscopic examination showed the tissue removed to be a foreign body, giant-cell tumor. Chemical analysis of this bone is recorded in Table 1.

It was during this fifth visit that attention was directed to the possible similarity of this case to the one reported by Barr, Bulger and Dixon. Many features were unmistakably similar: muscular weakness; rarefaction of bones; giant-cell tumors of bone; rather high blood calcium and low blood phosphorus; tumor

TABLE 4  
Metabolic Data for a Six-Day Period Before Operation\*

Date, 1928	Calcium in Urine, gm	Calcium in Stool, gm	Total Excretion of Calcium, gm	Phosphorus in Urine, gm	Phosphorus in Stool, gm	Total Phosphorus, gm	Blood Serum	
							Calcium, mg Per Cent	Phosphorus, mg Per Cent
December 10	0 22	0 053		0 509	0 068		12 79	1 98
11	0 31	0 038		0 587	0 042		11 84	2 07
12	0 31	0 091		0 680	0 121			
13	0 23	0 098		0 690	0 130		11 64	1 71
14	0 30	0 317		0 712	0 343			
15	0 31	0 121		0 714	0 124		12 44	2 11
Total (six days)	1 76	0 72	2 48	3 892	0 828	4 72		
Intake (estimated)			4 90			5 72		
Balance			+2 42			+1 00		

\*Patient receiving diet rich in vitamin D, also ultraviolet radiation

TABLE 5  
Metabolic Data for a Six-Day Period After Removal of a Parathyroid Tumor (December 17, 1928)

Date, 1928	Calcium in Urine, gm	Calcium in Stool, gm	Total Excretion of Calcium, gm	Phosphorus in Urine, gm	Phosphorus in Stool, gm	Total Phosphorus, gm	Blood Serum	
							Calcium, mgm Per Cent	Phosphorus, mgm Per Cent
December 18							9 06	1 71
19							7 73	
20							7 13	
21							8 28	1 99
22								
23							8 02	1 95
Total (six days)	0 084	7 25	7 41	1 78	1 62	3 40		
Intake* ?			+8 56			+5 30		
Balance			+1 15			+1 90		

\*An equal portion of all food eaten together with an equal dose of the calcium phosphate administered was to have been collected during this experiment. We are quite certain, however, that the food-drug mixture saved for analysis did not contain as much calcium or phosphorus as the patient actually received in medication. The positive balances therefore were probably greater than is indicated. The most striking features of this table are the almost complete suppression of calcium in the urine and the rapid fall of the calcium in the blood, both of which immediately followed the removal of the parathyroid tumor.

which had been interpreted as non-toxic adenoma of the thyroid gland, but which was now thought might be a tumor of a parathyroid gland. Operation for removal of the tumor was decided on, but before doing this the calcium in the urine and stool was determined for a period of six days (Table 4). Moderate retention of calcium and phosphorus was revealed.

December 17, a parathyroid tumor was removed. The immediate convalescence was satisfactory and the effect of the operation noteworthy. The blood calcium fell within three days almost to tetany values (Table 5). Actual tetany

TABLE 6  
Metabolic Data Three Months After Removal of the Parathyroid Tumor

Date, 1927	Weight of Body, kgm.	Hemoglobin (Dare), Per Cent	Erythrocytes for Each Cubic Millimeter	Blood Serum	
				Calcium, mgm. Per Cent	Phosphorus, mgm. Per Cent
April 3	45.0			8.33	1.8
4		46	4,920,000	8.16	1.6
5	45.5			8.41	1.8

did not occur, but the patient became generally nervous, and complained of numbness and tingling of the tips of the fingers and the toes. Calcium phosphate given by mouth relieved these symptoms. Marked suppression of calcium excretion occurred (Table 5) and the patient's strength improved rapidly, so that within two weeks she was able to abandon crutches and take walks of considerable length around the hospital grounds, merely with the help of a cane. She



Fig. 5. The skull, showing increase in the density of the bone three months after removal of parathyroid tumor. April 3, 1929. Compare with Figure 1.

left for her home January 7, 1929, with instructions to follow the diet rich in vitamine D, and to take 3 gm. of calcium phosphate twice daily.

A complete description of the gross and microscopic appearance of this tumor is published by Wellbrock in this issue of the Journal. He believes the tumor is a malignant adenoma. It measured 5 by 3.5 by 3 cm., and was situated at the lower pole of the right lobe of the thyroid gland. The other parathyroid glands were not examined.

The patient returned for re-examination, April 3, 1929, having adhered to the diet and calcium medication prescribed. She had been entirely free from pain and was walking comfortably, although still with the peculiar waddling motion. This was due probably to the wedge-shaped pelvis noted at a previous examination. Her weight was 45 kgm. (100 pounds) and her height 150 cm. Shortening of 2 cm. had occurred since the preceding visit, which was attributed to her being on her feet while the skeleton was still soft. Roentgenograms of the skull, spine, pelvis and femurs, when compared to those made before the removal of the parathyroid tumor showed unmistakably increased density, calcium deposit (Figs. 5 and 6). The blood serum calcium on three successive days was 8.33, 8.16 and 8.41 mgm., the corresponding inorganic phosphorus being 1.8, 1.6 and 1.8 mgm. (Table 6).

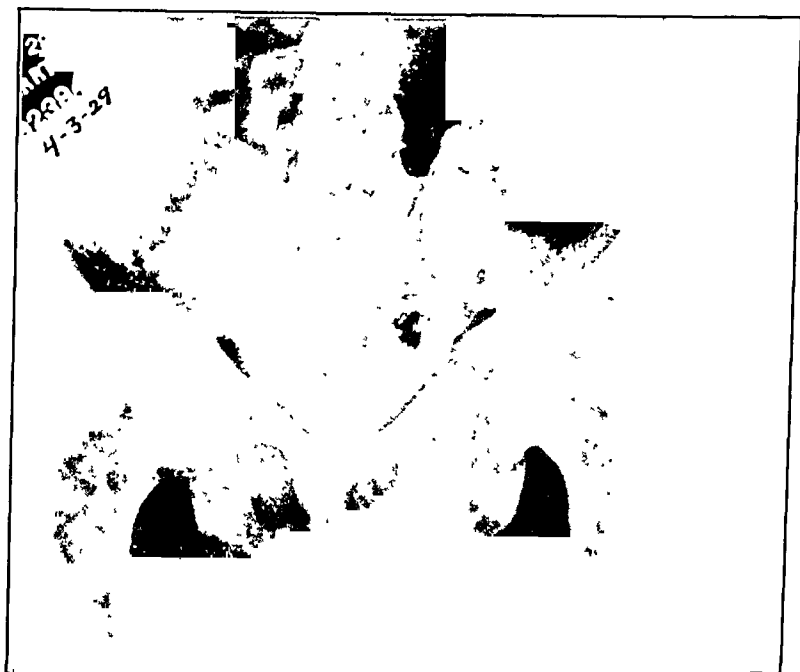


Fig. 6. The pelvis, showing increase in density of the bones three months after removal of parathyroid tumor. April 3, 1929. Compare with Figure 2.

#### METHODS OF CHEMICAL ANALYSIS

The calcium in the blood serum was determined by the Clark and Colip modification of the Tisdall and Kramer method.\* Phosphorus in the blood serum was determined by the method of Fiske and Subbarow. For the mineral balances, food equivalent to that eaten by the patient was dried and pulverized by its passage through a "mixtamal mill." Stools were dried according to the suggestions of Tisdall and Kramer. Aliquot portions of the urine for the period of study were evaporated in platinum. Direct ashing in platinum at low temperature, not exceeding 500 to 550 degrees C., was found to be the most satisfactory method of preparing these materials for analysis. Loss of phosphorus was not noted under the conditions; added phosphate was quantitatively recovered. The ash was taken up in 0.5 normal hydrochloric acid; phosphorus was determined by the Fiske and Subbarow method, calcium by the Tisdall and Kramer method as modified according to the suggestions of Shohl, and magnesium in the

\*I am indebted to Dr. M. H. Power and Miss Florence Wales for the chemical analyses in this case.



filtrate from calcium by precipitation as magnesium ammonium phosphate and determination of the phosphorus in the precipitate by the Fiske and Subbarow method.

#### COMMENT

In the cases of hyperparathyroidism thus far reported the disease was in adult men or women and produced either by tumor (adenoma or carcinoma) of a parathyroid gland or, as in the case of DuBois, by hyperfunction of otherwise normal parathyroid glands. The onset is insidious and the course chronic and progressive. The early symptoms are weakness and pain in the bones. As time passes debility increases until finally the victims are bedridden. The bones soften and the skeleton undergoes more or less deformity, such as wedge-shaped pelvis, scoliosis and loss of stature. Fractures may occur. Multiple swellings of bone are common, due to the formation of foreign body, giant-cell tumors. Renal calculi may develop with distressing urinary symptoms.

Secondary anemia is present. The electrical excitability of the muscles is reduced (hypotonia). An excessive excretion of calcium and phosphorus occurs, resulting in negative balances for these elements. This is associated with an increase in the calcium and a decrease in the inorganic phosphates of the blood serum. Roentgenograms show extensive diffuse rarefaction and what appear to be cysts of the bones. The latter on direct examination may be found to be foreign body, giant-cell tumors. Chemical analysis of the bones reveals considerable loss of calcium and phosphorus, and a relative if not an absolute gain in organic matter. The skeletal lesion is that described by von Recklinghausen as *osteitis fibrosa*, for which Stenholm has proposed the more appropriate term *osteodystrophia fibrosa*.

The disease is the antithesis of tetany (*parathyropriva*), exactly as hyperthyroidism is the antithesis of myxedema, and hyperinsulinism that of diabetes.

The fact that a tumor was not found by Richardson (7) in the parathyroid glands in the case of DuBois is interpreted as indicating that hyperparathyroidism may result from the hyperfunctioning of otherwise normal glands. An exactly analogous condition has been encountered in the case of the pancreas. The first patient with hyperinsulinism had a malignant tumor of the islets (32). In the next two cases of hyperinsulinism reported there were adenomas (20, 28). Since then two cases without tumor have been observed in The Mayo Clinic, and Finney and Finney have described a third case in which the clinical picture was essentially the same as that observed in the cases of tumor. Surgical intervention was undertaken in these cases for the purpose of removing a tumor. A tumor was not found, however, and large pieces of pancreas which were resected and examined histologically, contained perfectly normal appearing islets of Langerhans.

The study of cases of hyperparathyroidism may provide a clue to the nature of rickets. The clinical picture in rickets is not unlike that of *osteitis fibrosa* and in the common form of rickets the serum calcium is

excessive and the serum phosphorous deficient, as is the case in osteitis fibrosa. Tumors of the parathyroid glands have been reported in cases of rickets, and hyperplasia of the glands has been noted by Ritter, Pappenheimer and Minor in cases of rickets in man. In experimental rickets, hyperplasia of the parathyroid glands is the rule. Erdheim was the first in this field, but he has been followed by a number of others, the recent study of Higgins and Sheard being unusually suggestive. Nonidez and Goodale have shown that the parathyroid glands of chicks became enlarged when they were kept from direct sunlight on a ration poor in antirachitic vitamine. Higgins and Sheard confirmed this observation extending the study to a more detailed investigation of the wavelength of the light involved. They found that chicks growing under amber, blue or ordinary glass, which cuts out the ultraviolet rays, developed rickets early, and that with the rickets there was hyperplasia of the parathyroid glands. The diet of these chicks was poor in vitamine D. Higgins and Sheard found, further, that chicks similarly treated but given small, probably inadequate doses of ultraviolet radiation daily developed rickets only when they were more than six months old (late rickets), and that the hyperplasia of the parathyroid glands under these circumstances was associated with the formation of cysts. The cystic glands obtained by Higgins and Sheard resembled both in cells and structure, the adenoma of the parathyroid glands observed in the case of hyperparathyroidism reported here. The history of this patient suggests that during childhood an adequate supply of vitamine D was not obtained. Rickets was escaped during childhood, but, like the chicks of Higgins and Sheard, a clinical condition which resembled rickets developed later. Treatment with a diet rich in vitamine D and with ultraviolet light was carried out in 1927 and resulted in a marked gain in strength and in weight, improvement of anemia and retention of calcium and phosphorus. This is at least suggestive of some antagonism between vitamine D and activity of the parathyroid glands. It seems not unlikely that rickets, and osteitis fibrosa, may be due to overfunction of the parathyroid glands and that the healing effect of vitamine D in these conditions may be due to inhibition of the parathyroid glands by this vitamine.

It is impossible at the present time to explain the behavior of the serum calcium and phosphorus in hyperparathyroidism. In this case and in Barr, Bulger and Dixon's case, the former was elevated and the latter depressed before operation; after removal of the parathyroid tumor the calcium fell to low levels, whereas the phosphorus was unaffected. Particularly significant is the almost complete suppression of calcium in the urine which immediately followed operation and accompanied the precipitate drop of calcium in the blood. The phenomenon is not explained by any change in the proportion of diffusible to nondiffusible serum calcium, since the proportion was only slightly affected after operation for two days. The phosphorus in the urine was also depressed by the operation, but not to

the same extent as the calcium. There is no way of estimating whether or not the excretion of calcium and phosphorus into the bowel was diminished, since calcium phosphate was administered as a drug and much of this probably was not absorbed.

It is also impossible to account for the giant-cell tumors. These occurred in the case reported here and in that of Barr, Bulger and Dixon. Such tumors have been noted previously in association with osteomalacia and osteitis fibrosa. It is remarkably interesting that following parathyroidectomy in the case here reported a tumor of the maxillary bone disappeared, or at least decreased in size, to such an extent that it was no longer palpable.

From the experience already acquired with this new disease, it would seem desirable to recommend surgical exploration for tumors of the parathyroid glands in cases of skeletal decalcification of obscure cause, particularly if such decalcification is associated with hypercalcemia. If a tumor is found, it should be removed, and, if not, the removal of one or two parathyroid glands may be beneficial, as in the case described by DuBois and Richardson (7). It should be borne in mind, however, that this operation may be followed by a precipitate lowering of the calcium level of the blood and that the administration of calcium and possibly of parathormone may be necessary to prevent tetany.

#### SUMMARY

A case of osteitis fibrosa is described in which conditions attributable to excessive parathyroid activity occurred in association with a malignant parathyroid adenoma. The symptoms and data included progressive weakness, loss of muscle tone, anemia, pain in the bones, decalcification of the skeleton, associated with an increase of organic matter and foreign body, giant-cell tumors, hypercalcemia and hypophosphatemia. Four similar cases recently reported by others are described.

To some extent at least the disease is combated successfully by treatment with ultraviolet light and a diet rich in vitamine D. The suggestion is entertained that a rôle of vitamine D is the inhibition of the activity of the parathyroid glands.

The surgical removal of the parathyroid tumor in the case reported was followed by marked improvement in strength and muscle tone, relief of pain in the bones, increased calcification of the bones and the disappearance of a tumor of the maxilla.

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# ENDOCRINE STUDIES IN DEMENTIA PRAECOX

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In dealing with a disorder that has been discussed from so many and such diverse points of view as has dementia praecox it is expedient that one define somewhat explicitly the conceptions upon which his experimental attack and his interpretations are based. It is our belief that dementia praecox is a *reaction trend* and is an entity only and to a lesser degree in the sense that headache or fever is an entity. It is a disorder of multiple causation. Among the demonstrated "causes" of the psychosis are trauma, puerperal sepsis, typhoid fever and unresolved psychic conflicts. We share with Janet the belief that fundamental to the disorder in each case is a lack of nervous energy leading to a feeling of inadequacy and a consequent flight from reality. It can develop in a relatively strong man as a result of overwhelming difficulties or in a weak man from relatively trivial difficulties. To list the eminent psychiatrists who are in accord or disagreement with these conceptions, though conventional, would be supererogatory.

From these premises it follows that the numerous searches that have been made for *the* cause of dementia praecox were foredoomed to failure, and for precisely the same reason as would be a search for *the* cause of headache or sterility. The perennial debate whether the disorder is of organic or psychogenic origin is to our minds quite on a par with a discussion whether tuberculosis is due to the presence of tubercle bacilli or susceptibility of the patient. It disregards the nature of causality.

Our studies have been based upon the primary conception that dementia praecox is a reaction to a sense of personal failure arising primarily from a feeling of inadequacy to meet the issues of life as they actually present in a way to secure a tolerable degree of emotional repose. Any therapeutic attempts, therefore, should be directed to restoring a feeling of adequacy. The actual inadequacy is always relative. One could logically center his efforts on analyzing the psychic difficulties and attempting to remove these or re-educating the patient to conquer them. Likewise, he could logically center upon detecting and removing organic causes of the feelings of inadequacy. Neither, of course, should be neglected. It is towards the organic aspects of the problem that our endeavors have been primarily directed though with no feeling of disparagement of psychotherapy in its various conscious and unconscious guises.

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\*The expenses of this research have been met in part by The Memorial Foundation for Neuro-Endocrine Research, Boston.

That endocrine disorders occur in schizophrenic patients is indicated by the results of pathological and "constitutional" studies as well as by occasional reports of more or less complete amelioration of the psychosis following the correction of endocrine disorders. The literature on these topics has been discussed elsewhere (1). The question of the relative significance of endocrine factors, however, still demands much study.

For the past two years we have been engaged in such an investigation. An attempt has been made to determine: (a) the incidence of significant endocrine disorders in a random series of state hospital cases; (b) the results, mental and physical, of correcting, as far as possible, such disorders as were found; (c) the effects of empirical gland therapy in patients who were diagnosed "not demonstrably endocrine." This third phase of the investigation is partly a concession to the admitted inadequacy of available endocrine diagnostic methods and partly a control on the results of specific therapy.

#### METHODS

In general we have followed the methods evolved under the leadership of Rowe at the Evans Memorial in Boston (2). This angle of attack was adopted for three reasons: (a) we have been impressed with the practical utility of the methods in the hands of others; (b) we desired to subject the methods to an independent test; (c) irrespective of the validity of the methods their use involves the systematic collection of a large body of data on the physical and metabolic conditions of the patients such as is needed for an understanding of the organic aspects of the disorder from any point of view. The data have been collected under conditions permitting correlations to an extent that is not possible in case of scattered individual studies on various physiological or pathological processes.

In Table I is reproduced the "Summary Sheet" that is employed in tabulating the data. It serves in this connection to indicate the data secured. The general plan is to make a thorough initial study, securing data as complete as may be, not only on the features scheduled in the Table but also on the history and physical conditions of the individual patient.

For the most part no special comments on the technic employed in the various tests are necessary. Accepted standard methods are used. The blood samples are obtained before breakfast with care to avoid excitement. The Galactose tolerance tests are planned to avoid any wastage of this expensive sugar. In this, Rowe's technic (2) is followed exactly. The most difficult procedure in which to secure significantly reliable results is the determination of the basal metabolic rate. A closed circuit method is used (Benedict-Roth). The results are calculated to the Harris-Benedict and the Dubois standards and the average of the two is recorded. Tests are always made in duplicate and the better of the two utilized. If, as is usually the case, a satisfactory degree of repose is not secured on the first day, rehearsals are held until either the goal is attained or it has become evident that it is not then attainable. A critique on this phase of the work has been published elsewhere (3).

TABLE I  
VITAL FUNCTION TESTS

NAME	Psychiat. Diag.				Endocr. Diag.			
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment
Urine Amt. <sup>1</sup>								
Total Solids								
Total N.								
Urea N.								
Creatinin								
Residual N.								
Basal Metab. <sup>1 2</sup>								
Blood Pr. <sup>2</sup>								
Pulse <sup>2</sup>								
Temp. <sup>2</sup>								
Resp. <sup>2</sup>								
Blood								
Eryth. x 1000								
Leuct. x 100								
Poly leuc.								
Lymph.								
Eosin.								
Trans.								
Basoph.								
Blood Chem. <sup>2</sup>								
N. P. N.								
Urea N.								
Uric Acid								
Creatinin								
Sugar								
Ph. Sulph. Phth. <sup>1</sup>								
Galact. Tol.								
Weight								
Area								
Vital Cap.								
Urobil.								
Alv. CO <sub>2</sub>								
Urea Curve								
Van den Bergh, Dir.								
Vanden Bergh, Ind.								
Graham Test								
Bromosulph. 1 Hr.								
Stomach-time								
Colon-time								
Psychometric								
Psychotic Prog.								

<sup>1</sup>Tests made in duplicate.<sup>2</sup>Patients in bed.

During the progress of the tests or after their completion the patient is brought before the hospital staff and a psychiatric diagnosis and prognosis recorded.

The various data having been secured and analyzed, the patient, if his condition is not already well known, is placed under observation without treatment for one to three months. He is then either dismissed from further study or is subjected to one or more courses of gland therapy, with usually about three months' intervals between courses. At intervals of about six weeks one or more data such as the basal metabolic rate or others regarded as especially significant as indicating progress in the given case are re-determined and at intervals of about three months the complete series of vital function tests are repeated. Until recently no cases were dismissed from study on any ground except a degree of "spontaneous" improvement during the preliminary observation period or an initially favorable prognosis that would render any improvement under therapy impossible of evaluation. At the present time and in the light of the first year and a half of experience a certain degree of selection is employed to avoid the expenditure of our limited facilities on relatively unpromising cases. In general those patients with deeply fixed delusional systems and in whom the tests fail to disclose significant metabolic abnormalities are discarded.

Each week during the entire study a report on the mental condition of the patient is filed by a psychiatrist and each three days one by a psychologist who keeps in constant, close touch with the patients on the wards. Table II reproduces the form used by the psychologist in securing and recording his data. For this form we are indebted to Mr. A. T. Boisen. In many instances the actual time spent in various activities is recorded. The nurses, too, report their impressions of the patient each three days as well as whenever anything unusual occurs. They also record rectal temperatures and pulse rates twice daily and the weight each week. Occasionally significant observations are reported by workers in the Occupational Therapy Department. Recently arrangements have been made for further observations of the patients without their knowledge in a special recreation room. The psychiatrist and the psychologist usually remain intentionally in ignorance of the gland therapy and it is believed that their judgments are honest and unbiased. At intervals of about two months each patient is again brought before the Hospital Staff and progress, diagnostic and prognostic notes recorded. Table III, designed by Supt. W. A. Bryan, reproduces the form used to secure uniformity in these examinations.

The initial data on the individual case are summarized by the senior author and an endocrine diagnosis is made. Almost invariably both authors agree on the diagnosis but in case of disagreement both diagnoses are recorded and utilized consecutively in planning treatment. At intervals of one to two months the case is again summarized and modifications in the treatment made in accordance with the results of later tests and of the interim history.



## TABLE II

## WARD OBSERVATIONS

Name of patient.....Place.....Date.....

Observer.....Period of observation.....

APPEARANCE AND GENERAL BEHAVIOR (Neatness, output of energy, mannerisms, postures, etc.)

MOOD: Placid, complacent, cheerful, euphoric, elated, silly, facetious, boastful, irritable, suspicious, sad, hopeless, bitter, gloomy, anxious, perplexed, thoughtful, timorous, indifferent, apathetic, stuporous.

Variations:.....

SOCIAL ATTITUDE: Co-operative, amiable, submissive, self-assertive, antagonistic, sociable, seclusive, fault-finding, self-pitying, ego-centric.

WORK PERIOD: Kind of work.....Voluntary or compulsory?

Kind of suggestions or commands.....

Actual Work: Efficiency.....Steadiness.....Interest.....

Soldiering: Form.....

LEISURE PERIOD: Facilities available.....

<i>Social intercourse, with whom</i> .....	<i>attitude</i> .....
kind	steadiness      interest

Reading.....

Writing.....

Games.....

Reaction to success or failure.....

*Supervised play*—attitude.....actual participation.....

Kind.....steadiness.....interest.....

*Day-dreaming*

Facial expression.....physical posture.....

Evidences of response to hallucinations.....

Evidences of erotic indulgence.....

RESPONSE TO SPECIAL SITUATIONS: (i. e., visitors, letters, transfers, church, etc.).

SIGNIFICANT UTTERANCES AND BEHAVIOR OF PATIENT:

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TABLE III

## SCHEMA FOR STAFF REVIEW OF CASES

*General Appearance and Behavior*

Gait  
Clothing  
Attitude  
Facial Expression  
Mannerisms

*Speech*

Spontaneous or not	
Tone of voice	
Normal, coherent, relevant or	
Abnormal:	
Volubility	Verbigeration
Circumstantiality	Slowing
Distractibility	Retardation and Blocking
Neologisms	

*Mood*

Placid	Bitter
Cheerful	Sad
Elated	Hopeless
Boastful	Gloomy
Timorous	Anxious
Irritable	Perplexed
Indifferent	Apathetic
Suspicious	

*Orientation*

Time  
Place  
Person

*Memory*

Recent  
Remote

*Hallucinations*

Get full information  
When heard  
Men's or women's voices  
Do they talk to each other or to patient?  
Content of hallucinations  
Hallucinations other than auditory

*Compulsive Phenomena*

Impulses, compulsions, etc.

*Delusions*

When possible get full information relative to former ideas. Have the patient give an explanation of his conduct since the preceding progress note.

*Insight*

How far does the patient understand what is wrong?

*Diagnostic Summary*

The diagnosis should be checked at each Staff Meeting. This diagnosis must represent a majority vote (if any) of the Staff. The opinions of all must be recorded.

*Prognosis*

Should be recorded in the following terms:

## A. Complete Recovery.

This classification should be used for patients who will recover and be able to resume their place in the world. They should become self-supporting and without trace of former symptoms.

B. Social Recovery.

The individual can return to the community, become either fully or partly self-supporting, but will retain some of his symptoms under good control.

C. Institutional Social Adjustment.

The patient will be given a parole on the front wards, do some useful work, but cannot return to community life. He will retain his symptoms but have them under good control in the environment of the hospital.

D. Institutional Adjustment.

The patient will not be able to be trusted with any liberty but will remain clean and tidy, get along with other patients in the ward and do simple work.

E. Deterioration

The patient will gradually become untidy, antisocial or aggressive and violent, and do no useful work in the institution. He will remain inaccessible.

An element of personal judgment is unescapable in the assessment of degrees of improvement or regression. The lack of satisfactory quantitative criteria in the field is proverbial. One is forced to base judgment only on the considerations by which liberty or further confinement are habitually dealt out to psychotic patients the world over. As a matter of practical fact, whenever, in this study, the changes for better or for worse are in doubt the statement recorded is, "Not significantly changed." In evaluation of the various reports that make up the evidence, attention is directed predominantly to specific facts rather than to the impression of the observers. The special necessity of a critical attitude is constantly kept in mind.

In all, up to May first, 1929, eighty cases had been studied with sufficient thoroughness to permit an endocrine diagnosis, either definite or probable. The outstanding findings in the entire series are set forth in Table IV. The inadequacy of such tabular presentation will best be realized by those with the most extensive knowledge of psychiatry. Each entry is an attempt to epitomize a dossier of from 20 to 250 pages which, in turn represents an attempt to summarize the complex life of a human being. The most difficult phase of the undertaking is to determine in each case the prognosis. For example, the patient "J. P. K." when first seen was mute, resistive and stuporous, but the setting in which the picture was placed justified the favorable diagnosis initially recorded. This judgment was vindicated by the apparently complete recovery of the patient under ordinary hospital routine treatment. A rather similar picture in the case of "G. M.", in which the setting is very different, renders the prognosis practically hopeless. The "slight improvement" following the use of pluriglandular medication in this case is correspondingly more significant than would be a marked improvement in a case of initially good prognosis.

In general, it is our purpose to make a cross-section study of schizophrenia as seen in a state hospital population. While samples of most of

TABLE IV

SUMMARY OF CASES STUDIED TO MAY, 1929

CATATONIC TYPE

Patient Age	No. of Attack	Duration Years	Prognosis	Endocrine Diagnosis	Treatment	Psychiat. Results	Present Status
P. R. 46	2nd	5	Bad	Not. End.	Gonad Thyroid	None None	Discontinued
J. C. O.	1st	½	Fair	Not End.	Gon., Thy. & A. L. Pit.	Marked Impr.	At home
A. J. 22 2	1st	1 ½	Fair	Thyr. Def. (?)	Thyroid	None	Discontinued
N. C. 25	1st	5	Poor	Thyr. Def.	Thyroid	Improved	Removed
C. T. 21	3rd	½	Good	Not End.	None	Now well	At home
F. D. S. 34	1st	4	Poor	Thyr. Def.	Thyroid	Marked Impr.	At home
W. N. 24	3rd	1	Poor	Pit. Def.	None	None	On escape
J. P. K. 23	1st	¼	Good	Not End.	None	Marked Impr.	At home
T. L. H. 30	1st	2	Bad	End. Def. Uncl.	Thyroid	Slight* Impr.	Continued
D. I. 39	1st	5	Bad	End. Def. Uncl.	Thyroid	Marked Impr.	Continued
D. M. 24	1st	1	Poor	Not. End.	Gonad Gon., Thy. Thy. Adr. & Pit.	Improved None Sl. Impr.	Continued
G. M. 30	2nd	6	Bad	End. Def. Uncl.	Gon., A. L. Pit. & Thy. A. L. Pit. & Felamine Thy. Adr. Pit.	Sl. Impr. Impr. Cont. Sl. Impr. Maintained	Continued
C. M. N. 29	1st	4	Poor	End. Def. Uncl.	Lt. Thy. Heavy Thy.	Impr. More acute	Continued
D. R. 25	2nd	4	Poor	Not End.	Gon. & Thy. Gon., Thy. & Lt. A. L. Pit. Gon., W. G. Pit & Thy. Thy. W. G. Pit.	None Mod. Impr. Impr. Maintained More acute	Continued
A. R. 22	1st	5	Poor	Not End.	Gon. Thy. & A. L. Pit.	No change	Discontinued
D. S. 34	1st	½	Bad	Thyr. Def.	Lt. Thy. Heavy Thy.	No change Impr. cont.	Continued
G. F. S. 28	1st	3	Fair	End. Def. Uncl.	Lt. Thy. Heavy Thy.	No change Sl. Temp. Impr.	Continued
A. S. 20	3rd	¼	Bad	Pit. Def.	W. G. Pit. A. L. Pit. & Thy. Heavier W. L. Pit. & Thy.	Marked Impr. fol. by relapse No change	Continued
A. S. 23	1st	½	Bad	End. Def. Uncl.	A. L. Pit. W. G. Pit. Gon. & Thy.	Sl. Impr. More acute with clear periods	Continued
E. U. 24	1st	¾	Poor	Thyr. Def. (?)	Lt. Thy. Mod. Thy.	No change Marked Impr.	At home Apparently well
L. A. 26	1st	2	Poor	Pit. Def.	W. G. Pit. A. L. Pit. & Felamine	Improved Marked Impr.	Apparently well Continued

\*Minor degrees of improvement not carried forward into succeeding tables and disregarded in summaries.

Patient Age	No. of Attack	Duration Years	Prognosis	Endocrine Diagnosis	Treatment	Psychiat. Results	Present Status
A. A. 23	1st	5	Poor	Thyr. Def. (?)	Thyr. & Mag. Sulph. Thyr.	Marked Impr. Cont. Impr.	Apparently well Continued
B. B. 30	1st	½	Poor	Thyr. Def.	Mod. Thyr. Heavy Thyr.	Improved Marked Impr.	Non-psychotic sympt's Continued
H. O. P. 32	1st	¼	Good	Not End.	None	Improved	At home Apparently well
A. E. D. 24	1st	¼	Good	Not End.	None	.....	Discontinued

## HEBEPIRENIC TYPE

C. O. M. 20	2nd	1½	Bad	Not End.	None	None	Continued for observation
E. C. 26	1st	1	Poor	Thyr. Def.	None	.....	Discontinued
A. G. 26	2nd	½	(?)	Pit. Def.	A. L. Pit.	Sl. Impr.	At home
H. A. 32	1st	2	Fair	Not End.	Gon.	Sl. Impr.	At home
J. D. 23	1st	7	Poor	Pit. Def. (?)	Gon. A. L. Pit.	None None	Continued
A. F. 27	2nd	½	Bad	Thyr. Def.	Lt. Thyr. Heavy Thyr.	Sl. Impr. Increased Impr.	Continued
J. H. 22	3rd	½	Poor	Not End.	Thyr.	None	Continued
D. K. 19	1st	2	Poor	Pit. Def.	A. L. Pit. A. L. Pit. & Thyr. Heavy W. G. Pit. & Thyr.	None None More acute Sl. Impr.	Continued
B. M. M. 32	2nd	½	Poor	Not End.	Gonad	None	Discontinued
G. M. 29	1st	3	Bad	End. Def. Uncl.	Lt. Thyr. Gon. & A. L. Pit. Heavy Thyr. Gon. A. L. Pit. & Felamine	None Marked Impr.	Continued
J. N. 33	1st	1	Bad	Pit. Def.	A. L. Pit. Heavy W. G. Pit.	None None	Deteriorating 9 years Continued
C. S. 42	1st	4	Bad	Not End.	Lt., Mod. & Hvy. Pit. Thyr. & Gon.	None	Continued
C. W. S. 38	1st	1	Poor	Thyr. Def. (?)	Mod. Thyr. Heavy Thyr. Adr.	None More acute then Impr. None	Continued
G. S. 54	1st	10	Bad	Thyr. Def.	Lt. Thyr. Mod. Thyr. Heavy Thyr.	Mod. Impr. Impr. Cont. More acute	Continued
H. J. V. 33	1st	¾	Bad	Thyr. Def.	Adr.	None	Continued
V. C. 16	1st	½	Bad	Not End.	Thyr., Pit. Felamine	None	Continued
D. L. D. 28	1st	¼	Poor	Thyr. Def.	None	.....	New case Signs of Pit. Def.
T. M. 28	1st	5	Bad	Not End.	None	.....	New case
L. F. P. 38	1st	14	Bad	Not End.	None	.....	New case
E. C. P. 21	1st	1—	Poor	Not End.	None	.....	New case

## PARANOID TYPE

Patient Age	No. of Attack	Duration Years	Prognosis	Endocrine Diagnosis	Treatment	Psychiat. Results	Present Status
C. V. R. 37	1st	2	Bad	Not End.	Gon.	None	Discontinued
D. P. 31	1st	1½	Bad	Not End.	Gon. Thy., Pit. & Gon.	None None	Discontinued
D. M. 33	2nd	¼	Poor	Pit. Def.	A. L. Pit.	Sl. Impr.	Escaped
E. M. 35	1st	11	Bad	Not End.	Gon.	None	Continued
P. J. 38	5th	6	Bad	Pit. Def.	None	.....	Died after operation
E. A. J. 38	1st	1¾	(?)	Not End.	None	Improved	Discontinued
R. G. 33	1st	¼	Poor	Not End.	None	.....	At home
J. F. 37	1st	5	Poor	End. Def. Uncl.	Gon. A. L. Pit. W. G. Pit. & Thy.	None More acute More acute	Discontinued
J. F. 30	1st	1	Bad	Not End.	Gon. Thy., A. L. Pit. & Gon.	None None	Continued
R. H. 39	1st	4	Poor	Pit. Def. (?)	Gon. Gon. & Thy.	None None	Continued
A. H. 37	3rd	¼	Good	End. Def. Uncl.	None	Improved	Discontinued
J. T. S. 38	1st	1	Bad	Not End.	Gon. Adr.	None None	Continued
W. F. T. 35	1st	1½	Poor	Not End.	None	None	Discontinued
C. C. 22	2nd	½	Poor	End. Def. Uncl.	Gon.	None	Discontinued
O. D. 45	1st	3	Poor	Not End.	None	.....	New case
H. G. 44	2nd	1	Poor	End. Def. Uncl.	None	.....	New case
M. M. 47	2nd	4	Bad	Not End.	None	.....	Discontinued
J. E. T. 31	1st	4	Poor	Not End.	Gon. Pit., Thy. & —Gon. Heavy Gon.	None None More acute	Continued

## SIMPLE TYPE

A. B. 26	1st	2	Poor	Not End.	Gon. Gon. Thy. & A. L. Pit.	None None	Discontinued
L. Z. 25	1st	1	Poor	Pit. Def. (?)	W. G. Pit.	Mod. Impr.	At home
J. K. 57	2nd	13	Bad	Not End.	Gon. Gon. & Pit.	None None	Continued
E. O. 30	2nd	2	Bad	Not End.	Gon. Gon. & Thy. Thy. Gon. Pit.	Impr. None Further Impr.	Continued
D. E. S. 22	1st	½	Poor	Not End.	None	.....	New case
C. F. D. 39	2nd	½	(?)	Not End.	Gon.	None	Continued
T. D. 31	1st	½	Poor	P. L. Pit. Def.	P. L. Pit.	None	Continued

## UNCLASSIFIED TYPE

Patient Age	No of Attack	Duration Years	Prognosis	Endocrine Diagnosis	Treatment	Psychiat Results	Present Status
A B 21	1st	1½	B id	Not End	None		New case
H K 28	1st	9	Poor	Not End	None		New case
E K 21	1st	¾	Good	Not End	None		Discontinued
L A 22	1st	6¾	(?)	End Def Uncl	Lt Thy & Pit Heavier Pit	None Sl Impr	Continued
C E A 29	1st	1	Poor	Thyr Def (?)	Thyr Thyr & Adr	Mod Impr Marked Impr.	Continued
M C 27	1st	5½	(?)	P L Pit Def	P L Pit	None	Continued
B M 16	2nd	1½	Poor	End Def Uncl	None	Deteriorating	Continued
W C 36	2nd	¾	(?)	Not End	None	None	Escaped
F C 26	3rd	½	Good	Not End	None		Discontinued
J J O 35	1st	¾	Fair	Not End	None	Mod Impr	At home

Thyroid Deficiency		11
Definite	9	
Probable	5	
Pituitary Deficiency		13
Definite	9	
Probable	4	
Unclassified Endocrine Deficiency		13
Not Demonstrably Endocrine		40
Total Cases		80

the conditions found in such institutions are included, the study so far has been concerned more with recent than with chronic cases and it is lacking in examples of chronic, acutely agitated cases. It is planned to include these, ultimately, but this must be deferred until some sedative has been sufficiently standardized to permit evaluation of results secured with its aid.

The outstanding defect in the study to date is the lack of formal "controls" for the cases treated. Ideally, patients should be dealt with in pairs, as nearly similar as possible in age, duration of hospitalization, psychiatric type, background, mental symptomology and endocrine status. One of the pair should be given endocrine treatment and the other, a placebo, all other conditions being kept as nearly as possible identical for the two patients. Confronted as we were, however, with a large problem and relatively meagre resources, it seemed advisable first to undertake a general endocrine diagnostic and therapeutic survey in a sufficient number of cases to indicate whether the problem would be likely to repay further study. It was felt that if therapeutic results should prove consistently negligible an elaborate series of control studies would have been futile.

The work, however, has been by no means entirely uncontrolled. In a measure each patient serves as a control on himself in that his condition is

studied before and during treatment, as well as at intervals with treatment suspended. It is our impression that this type of control is not going to prove entirely satisfactory because of the seeming persistence of favorable results for considerable periods after suspension of treatment. Indeed, it is possible that a permanent cure may follow a single course of treatment. The best control feature in the work up to this time has been the use of a gonad preparation that has proved to be without significant influence (a commercial product, "Testacoids," said to contain extracts of testicle and prostate). Our earlier impression was that the material was of value and it was used with the same degree of thoroughness as was, for example, desiccated thyroid. In individual cases it was administered over a period of months and in varying dosages up to ten times that stated by the manufacturers as "indicated" in non-psychotic subjects. The fact that the prescriber anticipated an effect would serve to counteract any unconscious bias on his part in interpreting results. It served, therefore, as an ideal placebo.

TABLE V

## PRESENT STATUS OF CASES

NOT TREATED .....	27
Favorable prognosis or spontaneous improvement.....	9
Relatively unfavorable prospects for improvement.....	4
Dead or escaped .....	3
Under preliminary observations.....	11
TREATED .....	53
Under treatment, outcome not determined.....	33
Free from psychotic manifestations under treatment.....	4
Improved and sent home.....	5
Removed or escaped .....	2
Discontinued because of unfavorable prospects.....	9

A further control is obtained by a consideration of antecedent possibilities and the degree of consistency with which the data correlate with these. It is a matter of common experience that periods of improvement or even "spontaneous" cures are not infrequently encountered in dementia praecox—even, occasionally in patients with a poor prognosis. If, however, we were dealing only with changes of this type, the evidence of improvement should show a random distribution, irrespective of diagnosis or gland treatment. A segregation of the improvements in all groups treated with this or that substance would indicate that the material had a non-specific beneficial effect and that significant gland deficiencies did not occur. A segregation of incidences of improvement in groups diagnosed as specifically endocrinopathic and treated specifically would indicate both the validity of the diagnosis and efficacy of the treatment. Finally, frequency of improvement consonant with the known relative potency of gland preparations employed would afford confirmatory evidence on these latter points. The extent to which these possibilities have been realized will appear in consideration of Tables VIII to XI.



## RESULTS

With two exceptions, all the patients reported in this series were males, the ages ranging from 16 to 57 years, and the period of hospitalization from one month to 14 years (See Table IV). They were mostly "first admissions" but some had suffered from one to five previous attacks. "P. J.", who had had the most variegated hospital experience came to us lacking a colon, of which he had been deprived in a New Jersey institution. It remained for him to die in our hospital of peritonitis following a herniorrhaphy.

Of the 80 cases studied, 27 patients have received no treatment (See Table V). Of these, 11 are now in a preliminary observation period. Most of these, presumably, will be treated. In 9 cases the patients either had such favorable prognosis or progressed so well without treatment as to render them unsuitable for research purposes. Four were discarded as relatively hopeless and 3 either died or escaped before treatment could be given.

Fifty-three have received gland treatment. In 33 instances the cases are still pending with the outcome problematic. Three patients are still under treatment pending satisfactory arrangements for their dismissal from the Institution and one is being treated at home. Five have improved to the point that institutional care is no longer needed and have been sent home with treatment suspended. One has been removed and one has escaped during the progress of treatment. Nine have been discarded from the series as offering relatively too little hope to justify further study at this time.

TABLE VI

## ENDOCRINE DISTRIBUTION

<i>Types</i>	<i>Not Endocrine</i>	<i>Definitely Endocrine</i>	<i>Probably Endocrine</i>	<i>Total</i>
Catatonic .....	9	13	3	25
Hebephrenic .....	9	9	2	20
Paranoid .....	11	6	1	18
Simple .....	5	0	2	7
Unclassified .....	6	3	1	10
TOTALS .....	40	31	9	80
PERCENTAGES .....	50%	39%	11%	100%

The distribution of endocrinopathies among the various types of dementia praecox is shown in Table VI. The numbers are too few to be of more than suggestive value. The occurrence of 16 definite and probable instances in 25 catatonics, however, is striking and correlates with the fact that the incidence of improvement is highest in this group. Of the entire group 50 per cent have been diagnosed, "not endocrine," 39 per cent, "definitely endocrine," and 11 per cent, "probably endocrine."

The composite results of specific and non-specific treatment in various types are set forth in Table VII. As would be anticipated by those familiar with the results of other types of treatment in schizophrenia the highest

incidence of significant improvement, 62 per cent, occurred in the catatonic group and the lowest, 14 per cent, in the paranoid group. The series is not yet sufficiently extensive to justify formal "partial correlations," nor are the absolute percentages to be taken as of more than suggestive value.

TABLE VII

## RESULTS OF TREATMENT IN DIFFERENT PSYCHIATRIC TYPES

<i>Type</i>	<i>Number Treated</i>	<i>Number Improved</i>	<i>Percentage Improved</i>
Catatonic .....	21	13	62%
Hebephrenic .....	14	5	36%
Paranoid .....	14	2	14%
Simple .....	5	2	40%
Unclassified .....	3	1	33%
TOTAL .....	57	23	40%

In Table VIII are shown the results of substitutive gland treatment in 23 cases in which definite or probable diagnoses of specific gland hypofunction were made. No instances of diabetes mellitus nor of frank adrenal deficiency were encountered. Since all the patients treated were males and since Rowe's diagnostic methods, which we used, fail to define gonad deficiency except in women, this group includes only cases of thyroid and of pituitary deficiency. In all but one of 11 cases of thyroid de-

TABLE VIII

## RESULTS OF SPECIFIC THERAPY

	<i>Treated</i>	<i>Improved</i>	<i>Percentage</i>
Thyroid Deficiency—definite .....	6	6	100%
Thyroid Deficiency—probable .....	5	4	80%
TOTAL .....	11	10	91%
Pituitary Deficiency—definite .....	7	2	29%
Pituitary Deficiency—probable .....	5	1	20%
TOTAL .....	12	3	25%

fiency unquestionable improvement occurred. This ranged in degree from better contact and greater cooperation to apparently complete freedom from the psychosis. A striking observation in this series is that schizophrenic patients apparently have, as a rule, a remarkably high tolerance for thyroid substance. It proved necessary in some cases to administer 40 to 60 grains of potent desiccated substance daily to secure clean cut functional effects such as accelerated pulse rate or increased basal metabolism. Even higher doses were used for brief periods in certain cases without harm to the patients. Whether the high tolerance is due to depressed assimilation or to actual metabolic anomalies has not yet been determined. The matter will presumably be settled by the substitution of thyroxin by vein for gland substance by mouth.

The relatively low incidence of significant improvement, 25 per cent, under pituitary medication is probably to be ascribed to the relative lack

of potency of this substance when taken by mouth. It is probable, too, that the dosages used in our studies have been for the most part inadequate though we have given up to 60 grains of the dessicated substance daily. We have made a few experiments with hypodermic injections of posterior lobe extract and have begun the use of enteric coated tablets, but the experience has not yet been sufficiently extensive to justify any surmises as to probable results.

TABLE IX  
RESULTS OF GLAND TREATMENT IN UNCLASSIFIED ENDOCRINOPATHIES

	<i>Treated</i>	<i>Improved</i>	<i>Percentage</i>
Thyroid Treatment .....	5	3	60%
Pituitary Treatment .....	2	0	0%
Gonad Treatment .....	2	0	0%
Pluriglandular Treatment .....	4	2	50%
TOTAL .....	13	5	38%
ENDOCRINOPATHIES, GRAND TOTAL.	36	18	50%

In thirteen cases, as indicated by Table IX, the deviations in the vital function tests were sufficient in degree and number to justify a diagnosis of endocrine deficiency, but the pictures were not sufficiently characteristic to permit allocation of the difficulty to any one gland. Therapy, therefore, had considerably more of the random element than in case of the preceding series. In three of five instances thyroid proved efficacious and in two, pluriglandular treatment. This latter included thyroid, pituitary and gonad or adrenal substances. It is probable that truth would not be greatly violated if these two instances were allocated to the thyroid component.

In Table X is shown the incidence of improvement in 39 cases diagnosed as "not demonstrably endocrine." In 11 of these patients thyroid was used without a single instance of significant improvement, whereas all

TABLE X  
RESULTS OF GLAND TREATMENT IN NON-ENDOCRINE CASES

<i>Gland Material</i>	<i>Treated</i>	<i>Improved</i>	<i>Percentage</i>
Thyroid .....	11	0	0%
Pituitary .....	9	1	11%
Gonad .....	17	2	12%
Pluriglandular* .....	2	2	100%
TOTAL .....	39	5	13%

\*In case of negative results each gland is scored whether used singly or in combination. In case of positive results in glandular combinations and in which the effective component has not been determined the improvement is attributed to the combination as such. In cases in which the effective component is indicated by the results of successive additions or eliminations the improvement is credited to the individual gland.

but one of 11 patients initially suffering from definite or probably thyroid deficiency seemingly profited from its use. This contrast seems entirely too sharp to be ascribed to coincidence. Such clear cut differential results are hardly to be expected in a more extensive series of cases, uniformity not being the habit of biological data. In the entire series of "non-endo-

crine" cases, favorable developments followed the use of gland products in but 13 per cent of the cases as contrasted with 50 per cent in the endocrine group.

The data of Tables VIII, IX and X, as regards thyroid, pituitary and gonad medication, are rearranged in Table XI to permit easy comparison. It is seen that 13 of 23 cases of definite endocrinopathy (57 per cent) showed improvement following specific therapy. Three of 9 cases of un-

TABLE XI  
EFFICACY OF INDIVIDUAL GLANDULAR PREPARATIONS  
NUMBER OF CASES IMPROVED

<i>Material Used</i>	<i>Specifically Indicated</i>	<i>In Unclassified Endocrinopathies</i>	<i>In Non-Endocrine Cases</i>
Thyroid.....	10 of 11 cases	3 of 5 cases	0 of 11 cases
Pituitary.....	3 of 12 cases	0 of 2 cases	1 of 9 cases
Gonad.....	.....	0 of 2 cases	2 of 17 cases
Pluriglandular.....	.....	2 of 4 cases	2 of 2 cases
TOTAL—Uniglandular...	13 of 23 cases 57%	3 of 9 cases 33%	3 of 37 cases 8%
TOTAL—including Pluriglandular.....	.....	5 of 13 cases 38%	5 of 37 cases 13%

classified endocrinopathy (33 per cent) showed improvement on random gland therapy, whereas in only 3 of 37 non-endocrine cases (8 per cent) were favorable changes noted after similar monoglandular random therapy. The inclusion of 2 cases in which improvement followed the use of pluriglandular therapy would raise this proportion to 5 in 39 cases or 13 per cent. As they stand the data indicate as definitely as can be indicated in a series so restricted in numbers, that endocrine deficiency occurs in a high percentage of cases of dementia praecox, that these endocrinopathies can be detected by metabolic studies and that the patients frequently respond favorably to specific gland therapy.

The study has brought out another significant fact, namely, that endocrine deficiencies as they occur in schizophrenic patients are seldom of sufficient degree to produce the classic stigmata of these conditions. In few instances have sufficient degrees of obesity, for instance, been noted to raise even a suspicion of endocrine involvement and in no case was myxedema present. On the other hand, depressed basal metabolism occurred with notable frequency, as did low temperature and blood pressure, in the "non-endocrine" as well as the "endocrine" cases. These latter evidences of metabolic depression proved amenable to thyroid therapy in various instances, but corresponding mental improvement occurred only in the "endocrine" group. The temptation is strong to discuss the possibility that adrenal or gonad deficiency might account for these depressions, but since we have had available no potent preparations of these glands the possibility could not be put to therapeutic test and such discussion at this juncture would hardly be profitable.

A possible vitiating factor in these statistics, namely, an accidental occurrence of relatively favorable initial prognosis in the group that re-

sponded favorably to thyroid treatment must be considered. As a matter of fact, it happened that the prognosis originally recorded was "bad" in 4 cases and "poor" in 6. Paradoxically, in the one case in which no significant improvement was noted, the initial prognosis was "fair."

As will be seen from Table IV, in a few instances adjuvants to the gland substances were used, namely, magnesium sulphate or "Felamine," a commercial preparation containing bile salts. So far as could be determined, these adjuvants were not significantly influential. In any case, however, the instances of such use were too few to make any significant differences in the statistics of the group as a whole.

In Table IV, too, are recorded several instances in which the symptoms became more acute following the administration of gland substances. Since schizophrenics are characteristically subject to "ups and downs," a certain number of such instances might be expected irrespective of gland treatment. Whether the treatment was actually a factor in such exacerbations our statistics are too few to indicate. Perhaps the most ominous feature in a schizophrenic psychosis is the passive acceptance of it by the patient. When he is no longer troubled by continued delusions or hallucinations, he is well on the way to dissolution. The recurrence of evidences of acute conflict, therefore, could theoretically be regarded as a favorable rather than an unfavorable development. As a matter of fact, whether as a coincidence or not, in several cases in which marked improvement occurred, it dated from the subsidence of a state of increased mental tension marked by irritability, noisiness, assaultiveness, etc.

The extent to which the mental improvement can be carried by gland treatment in the patients that react favorably remains to be determined. As previously mentioned, the term "improved" includes all degrees in which the change was sufficiently marked to be unquestionable. Thus, "G. M." had been mute, uncooperative, silly, grimacing—in short, generally dilapidated—for so long as to have been, by common consent, relegated to the ranks of approaching dissolution. He is still deeply immersed in his psychosis. He has, however, stopped grimacing and become able to make his wants known. He is more alert and friendly and there is now at least a fair hope that he will escape the final deterioration, to which he was apparently doomed. "A. A.," on the other hand, who was assaultive, silly, exhibitionistic, mute—in short, a ward nuisance—is now a trusted orderly in the hospital, apparently free from his psychosis and ready to go home as soon as suitable arrangements can be made. Whether this will prove to be a case of striking remission or a permanent cure time alone will tell.

Being mindful of the history of therapeutics we are disposed to make wide allowances for the "long arm of coincidence." Our series is not yet sufficiently extensive nor has sufficient time elapsed in any case to permit unqualified claims or final conclusions. The work is presented merely as offering at this time substantial hope.

## SUMMARY

A metabolic study has been made of 80 subjects of dementia praecox.

Of these, half gave definite or presumptive evidences of endocrine gland deficiency. In 14 cases the thyroid gland was involved and in 13, the pituitary. In 13 others the specific gland at fault was not determined.

Fifty-three of the 80 patients received gland treatment. In the endocrinopathic group half showed significant mental improvement. In the non-endocrine group only 5 instances of similar improvement were seen in 39 experiments.

Following the gland treatment 5 patients became well enough to go home and treatment was suspended. One is continuing treatment at home and he, as well as 3 others still in the hospital, are nearly or completely free of psychotic manifestations.

The highest incidence of improvement has been noted in the catatonic and the lowest in the paranoid group. This is possibly correlated with high incidence of thyroid deficiency in the catatonic, and of pituitary deficiency in the paranoid subjects.

Of the gland substances employed, thyroid proved most efficacious. Mental improvement followed its use in 10 of 11 cases diagnosed as hypothyroid. In 11 non-endocrine cases none showed significant mental improvement following thyroid medication, though it served to correct certain physical conditions such as secondary anemia or reduced basal metabolism.

The use of pituitary preparations by mouth was followed by improvement in 3 of 12 cases diagnosed as of pituitary deficiency. It is probable that the dosages were inadequate.

The gonad preparation used gave no significant evidences of efficacy.

In only 3 of 37 "non-endocrine" cases were instances of significant mental improvement noted following the use of thyroid, pituitary or gonad substances alone. Two others improved on pluriglandular therapy.

The degree of improvement ultimately to be expected from the use of gland substances has not been determined nor can the permanency of such improvement as has occurred as yet be stated.

It is concluded that endocrine deficiency plays a significant rôle in dementia praecox and that in properly selected cases specific endocrine therapy is of value in the treatment of this disorder.

It is a pleasant duty to express our appreciation of help from many members of the Hospital community. We are particularly indebted to Supt. W. A. Bryan for his unvarying cooperation; to Drs. N. Barrett and M. Yorshis, who have served as ward psychiatrists; to Mr. A. P. Guiles, who has made many of the ward observations; to Mr. A. T. Boisen, many of whose case analyses we have utilized and whose abundant experience has been placed at our disposal in securing illuminating evidence of the behavior of the patients; to Miss A. Walsh, under whose supervision the technical laboratory procedures have been carried out; to Dr. R. Hunt, who has served as consulting chemist; and to Mr. H. Dragon, who, as Supervisor of Nurses, has aided in smoothing out many ward difficulties. Our especial thanks are due to Dr. A. W. Rowe for generous cooperation and frequent advice in the use of his diagnostic methods.

We are indebted to Armour and Co. for a part of the thyroid and pituitary material used in this work.

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# STUDIES OF THE ENDOCRINE GLANDS. VIII

## Protocols of Non-Endocrine Cases Simulating Endocrinopathies

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In a preceding paper\* of the series of which this communication forms a part, the importance of differentiating true endocrinopathies from other cases simulating them was discussed. Herewith are presented a number of case protocols in illustration of some of the interesting categories that have come to our attention.

### GROUP I. CASES SIMULATING SOME TYPE OF THYROID DISEASE

**CASE B-329.—PARALYSIS AGITANS SIMULATING HYPERTHYROIDISM.** The patient was a man 57 years of age, emaciated, presenting as his chief complaint a coarse tremor of the extremities, difficulty in speech, and pain in the muscles of the legs and shoulders. Eight years previously he had remarked a slight hesitancy in raising the right hand, coupled with a pain in the right shoulder. During the following year he developed extreme fatigability, and one year after the onset of the condition he noted an intention tremor of the hand, which progressed unfavorably during the next two years. He then noticed a slight dragging in the right foot and was told that he had an abscess on the brain. His reaction to this news was a complete nervous breakdown during which all of his symptoms were exaggerated. Still another year later he developed pain in the chest, burning sensations in the right leg and right side of back. A winter in California produced a larger measure of comfort, but no real improvement in the symptoms. A few months before we saw him the left side became involved, pain and lameness increased and speech defects appeared. He had lost 15 pounds in the past eighteen months, but there had been an earlier loss in the preceding years of the condition. The face had become mask-like, the eyes noticeably staring and the tremor extensive and coarse in both arms and legs.

*Family History:* The patient's father died of cancer; the remaining history was negative.

*Past History:* The patient reported the usual children's diseases and an attack of typhoid three years before the onset of his illness. He had been married for 17 years; his wife had borne one child without miscarriage. He complained of some vertigo. The hearing was impaired on the right side and there was a right-sided partial nasal obstruction. He experienced tinnitus, some dyspnoea during the past year and had been constipated for a long time. Some urinary frequency and urgency, marked fatigability as already noted, and occasional cramps.

*Physical Examination:* The patient was a tall, emaciated individual 57 years of age, with a mask-like expression and a marked tremor of all of the extremities. The right pupil was slightly larger than the left, there was a slight diver-

\*Lawrence, C. H. and A. W. Rowe: This Journal, 13: 109. 1929.

gent strabismus and lateral nystagmus, a minor cervical adenopathy, slight increase in the breath sounds at the right apex, and sluggish knee jerks. A state of tonus in the extremities, and an inability to spread the fingers of the right hand were also noted.

TABLE XVIII  
Simulation of Thyroid Disease

	1	2	3	4	5	6
Case Number.....	B-329	B-481	B-552	B-809	B-883	S-1057
Sex.....	M	F	F	M	M	M
Age.....(yrs.)	57	50	47	57	13	29
Height.....(cm.)	176	155	165	182.5	156.5	176.0
Weight.....(kgm.)	53.4	31.4	43.6	69.8	44.0	53.7
Weight Deviation.....(%)	-24	-38	-28	-12	-14	-26
Lung Volume Deviation.....(%)	-43	-33	-32	-13	-5	-11
Basal Rate Deviation.....(%)	+105	+49	-25	-15	-20	+7
Blood Pressure.....(mm.)	136/62	112/56	145/72	110/65	102/54	110/58
Pulse Rate.....(per min.)	72	100	68	56	78	72
Temperature.....(deg.)	96.8	98.0	99.0	98.0	99.0	98.0
Alveolar CO <sub>2</sub> .....(mm.)	43	41	41	42	44	38
Urine Volume.....(cc.)	620	510	690	1480	730	2430
Spec. Grav.....	1.021	1.028	1.012	1.015	1.010	1.014
Albumin.....	+	+	0	+	+	0
Casts.....	0	0	+	+	0	0
Sugar.....	0	0	0	0	0	0
"Urobilinogen".....	0	0	+	0	0	0
Total Nitrogen.....(gm.)	6.48	7.91	3.31	10.30	3.32	15.35
Residual Nitrogen.....(%)	8.3	18.3	13.9	9.4	11.0	7.7
P. S. P. (2 hours).....(%)	56	58	..	56	54	63
Galactose Tolerance						
Normal.....(gm.)	30	30	30	30	30	..
Observed.....(gm.)	10	10	30	30	30	..
Deviation.....(%)	-67	-67	±0	±0	±0	..
Blood						
N. P. Nitrogen.....(mgm.)	33	42	36	33	32	32
Uric Acid.....(mgm.)	3.3	3.7	7.1	2.9	3.3	3.1
Sugar.....(mgm.)	109	68	95	89	94	104
Haemoglobin.....(%)	75	80	30	85	100	85
Erythrocytes.....(10 <sup>6</sup> )	5.30	3.70	1.20	4.35	5.41	5.84
Color Index.....	0.71	1.08	1.25	0.97	0.92	0.73
Leukocytes.....(10 <sup>3</sup> )	5.2	82.9	6.7	8.2	9.7	6.8
Neutrophiles.....(%)	50	5	62	65	46	75
Lymphocytes.....(%)	44	56	33	23	42	20
Eosinophiles.....(%)	0	2	0	3	3	1
Endothelials.....(%)	6	1	2	8	9	4
Misc.....(%)	0	*36	3	1	0	0
Wassermann.....	0	0	0	0	0	0
Spinal Fluid.....	—	—	—	0	—	—

\*Myelocytes.

1. Paralysis agitans simulating Hyperthyroidism.
2. Myelogenous Leukaemia simulating Hyperthyroidism.
3. Primary Anaemia simulating Hypothyroidism.
4. Lesion of central nervous system simulating Hypothyroidism.
5. Pulmonary Tuberculosis and Epilepsy simulating Hypothyroidism.
6. Pulmonary Tuberculosis referred for Hyperthyroidism.

*Laboratory Summary:* The patient was 24 per cent below his predicted weight, and there was a marked and significant loss of lung volume. The basal rate was 105 per cent above prediction, systolic blood pressure was normal, but the pulse pressure was large. The pulse rate was normal, body temperature sub-normal. The urine volume was small, elimination poor; albumin present. Protein intake was below a maintenance level. Residual nitrogen showed an upward tendency. The sugar tolerance was much depressed. The blood chemistry was substantially normal. He had somewhat low haemoglobin and a distinct relative lymphocytosis. The blood calcium was definitely depressed; blood coagulation time somewhat retarded. Radiograms of the skull, sella and sinuses were negative. A Barany test was requested, but it was felt unwise to attempt it in view of the patient's physical condition. An audiogram showed a definite



loss of hearing in both ears. The eye examination gave sluggish pupillary reactions, yellowish discs, enlarged blind spots, and a slight loss in the form fields. Neurological examination defined the condition as a true paralysis agitans.

*Discussion:* The whole general picture here contains, superficially, at least, many suggestions of a hyperthyroid condition. The patient's loss of weight, tremor and slight but definite exophthalmos, were suggestive. The high basal rate, large pulse pressure, lowered sugar tolerance, definitely lowered lung capacity, were all consistent with a definite degree of thyroid overactivity. His high basal rate derived, of course, from the muscular tremor; the lowered sugar tolerance from a lesion of the central nervous system connected with his disability. A review of his laboratory tests without the clinical picture would inevitably have led to a diagnosis of hyperthyroidism, the only contradictory feature being the normal pulse rate. This case is one in which the laboratory work was of no great significance. The clinical examination determined the diagnosis, and the laboratory work was of value only in its ability to eliminate the presence of some intercurrent condition.

**CASE B-481—MYELOGENOUS LEUKAEMIA SIMULATING HYPERTHYROIDISM.** The patient was a woman of fifty, referred for study, offering abdominal pain as the chief complaint. This latter had occurred suddenly a week prior to admission and the examination by her physician demonstrated a splenomegaly.

*Family History:* A prevalence of heart disease in several immediate relatives was the only point worthy of notice.

*Past History:* The patient reported the usual ailments of childhood, a severe attack of influenza at the time of the epidemic, and pneumonia two years previously. An appendectomy eight years previously had corrected the frequent attacks of nausea and vomiting from which the patient had previously suffered. She had been married for 26 years and had borne one child by operative delivery. There was no history of miscarriages. Following the birth of the child there had been rare but severe attacks of vertigo. Of later years the patient complained of loss of hair. The eyes were said to fatigue easily. There was an earlier history of earache and discharging ears. Recently nasal obstruction had developed, with slight epistaxis on blowing the nose. A number of teeth had been removed. She had had marked dyspnoea for several years; had been extremely fatigable for about the same period and had severe night sweats during the past winter with a gradual loss of weight over a period of four years. She reported some nocturia and had noticed that the urine was very dark during the past year. The onset of catamenia was at 16 and the function was regular and normal up to the birth of her child. Following this there was an occasional period of metrorrhagia, usually with pain. There had been an abrupt menopause at the age of 46. She had suffered from leukorrhoea since the establishment of the menses. She was disposed to date all of her difficulties from the birth of her baby 25 years before, and since that time she had had to work hard and had worried over various domestic problems. She acknowledged a degree of emotional instability and complained of formication and occasional tremors of the hands and arms.

*Physical Examination:* The patient was a frail, poorly developed and undernourished woman of 50; the ear drums were distinctly thickened but hearing was seemingly unimpaired. There was some crusting in the nares, a number of teeth were missing and the remainder were in poor condition. The tonsils were slightly enlarged. There was a slight increase in tactile fremitus in the region of the left scapula, but the lungs were otherwise normal. The heart was apparently of normal size, the sounds somewhat muffled, no murmurs were remarked; there was a slight sclerosis of the peripheral vessels. The abdomen was slightly distended on the left side, and a large tumor mass, apparently the spleen, was demonstrated. There was also some hepatic enlargement. There were some telangiectases on the extremities. The skin was pallid, and there was a slight yellowish perspiration of unpleasant odor which stained the bed linen. There were superficial lymph nodes, large and hard, all over the body. There was a suggestion of a positive Babinski, bilaterally, the abdominal reflexes were rather less active on the left, the remaining routine neurological observations were normal.

*Laboratory Summary:* The patient was 38 per cent underweight and showed a significant loss of lung volume. The basal rate was 49 per cent above predic-

tion with rapid pulse, somewhat low systolic blood pressure, and relatively large pulse pressure. The urine was scanty and contained albumin. The residual nitrogen fraction was over 100 per cent above the normal. The sugar tolerance was markedly depressed. The non-protein nitrogen of the blood was above the normal. The blood sugar value as reported was low but this was undoubtedly due to the rapid loss of blood sugar after the removal of the blood, which is characteristic of the leukaemias. The blood morphology gave a characteristic picture of myelogenous leukaemia with 36 per cent myelocytes and a white count of over 80,000.

*Ear Examination:* No evidence of disease was found beyond the loss of hearing already noted.

*Pelvic Examination:* The fundus was normal in size, somewhat fixed, and manipulation produced pain. There was laceration of the cervix.

*Nose and Throat Examination:* The findings were substantially normal.

*Neurological Examination:* There was no evidence of organic neurological disease. The positive Babinski tests were not confirmed.

*Eye Examination:* Yellowish discs, enlarged blind spots, and some symmetrical contraction of form and color fields, were noted.

*Roentgenogram:* The spleen was greatly enlarged.

*Discussion:* The general laboratory picture here presented, the small urine volume, high residual nitrogen, basal rate well above prediction, rapid pulse, relatively large pulse pressure, increased non-protein and urea nitrogen, normal uric acid, depressed sugar tolerance and significant loss of lung volume definitely suggests a hyperthyroid condition. In this case, of course, the blood picture served as a check on the laboratory findings and prevented an erroneous diagnosis from the laboratory material alone. Naturally the physical examination again prevented error in the classification of the case. With these two exceptions, however, the parallelism between the laboratory observations of the endocrine and non-endocrine conditions is rather striking.

**CASE B-552—PRIMARY ANAEMIA SIMULATING HYPOTHYROIDISM.** The patient's chief complaint was of increasing fatigability and weakness which had first been remarked a year previously. In the course of a few weeks she developed pain in the legs with numbness and tingling in the extremities. Under medical care there had been temporary improvement, but for several months prior to admission she had been growing progressively weaker and for two months she had been confined to her bed.

*Family History:* A twin sister had died of primary anaemia. The remaining family history was irrelevant.

*Past History:* The patient reported the incidence of several of the minor ailments of childhood, scarlet fever and diphtheria during this period, and influenza at the time of the epidemic. Seven years previously she had been cured for excessive flowing. She complained of a rare headache, some vertigo during the past month, this latter accompanied by photophobia, and some postorbital pain, and gave a history of earlier hay fever which had apparently corrected itself spontaneously, and the earlier removal of several abscessed teeth. During the past month there had been marked dyspnoea, and an occasional night sweat. A year previously there had been a rapid loss of weight (18 pounds). She further reported some nocturia, a rare gastric disturbance, occasional constipation, and poor appetite. The catamenia was established at the age of 16, the periods were somewhat irregular with increase in the interspace and an abrupt cessation five years previously at the age of 42, following a three weeks' period of menorrhagia.

*Physical Examination:* The patient was a fairly well-developed but much under-nourished woman of 47. The lips were pallid and the face had a decided yellow lemon tinge, the tongue was not abnormally smooth and presented a slight tremor on protrusion. There was a loud systolic murmur over the aortic and mitral area, transmitted to the axilla and scapula, as well as a slight diastolic murmur at the apex. A minor cervical adenopathy was remarked. She had a slight kyphosis and lumbar lordosis; coordination was poor in all of the extremities, bone conduction was lost over the tibiae, arms and legs were spastic, knee jerks were increased, certain other reflexes absent, the Babinski was positive, and there was bilateral ankle and patella clonus.

*Laboratory Summary:* The patient was 28 per cent underweight and sub-

stantially below her predicted lung volume. The basal rate was 25 per cent below prediction. The blood pressure showed varying values, that recorded being representative. There was a slightly febrile temperature. The urine volume was scanty; albumin was not observed. Both hyaline and epithelial casts were found in the sediment. The "urobilinogen" test was positive. The sugar tolerance was normal. Non-protein nitrogen was at a slightly high level. The blood uric acid was almost double the normal value. The blood morphology gave a picture characteristic of primary anaemia or one of the simulating conditions. There were two microblasts, thirteen normoblasts, and two megaloblasts, in a count of 200, together with 3 per cent of neutrophilic myelocytes.

*Stool Examination:* No Bacilli Welchii, no blood, ova or parasites were found.

*Cardiogram:* The tracings were normal.

*Heart Examination:* Systolic murmurs were verified and ascribed to the anaemia.

*Pelvic Examination:* Normal.

*Neurological Examination:* There was a spastic ataxia syndrome of the lower extremities with Babinski, ankle and patella clonus. Deep sensation was interfered with over the lower extremities, the abdominal reflexes were absent.

*Eye Examination:* The discs were yellowish in color, the blind spots slightly enlarged.

*Discussion:* Practically all of the laboratory findings were consistent with hypothyroidism. The low basal rate, naturally, derived from the patient's partial inanition. The urobilinogen, so called, has been observed by us in several cases of primary anaemia and also in those cases of thyroid failure associated with a dysfunctional state of the liver. The somewhat high blood pressure is of the order frequently observed in the late stages of thyroid failure with marked arteriosclerotic changes. The normal sugar tolerance was likewise suggestive, as was the lowered permeability of the kidney indicated in the blood and urine examination. A urea curve gave a much delayed elimination, which again would suggest a thyroid failure. The high blood uric acid was anomalous for the endocrine condition. Of the current laboratory tests the blood morphology was the only one sharply defining in character, and this was supported by the neurological findings. A gastric analysis was not made on this case because of the weakness of the patient and the substantial establishment of the diagnosis by the facts recorded.

**CASE B-809—A LESION OF THE CENTRAL NERVOUS SYSTEM SIMULATING THYROID FAILURE.** The patient's chief complaint was of persistent headache from which he had suffered since early childhood. At the age of 8 he had an illness which was diagnosed as spinal meningitis in which severe headache was one of the presenting symptoms. This latter persisted after his recovery from the illness. During his earlier life it was occipital and basal in type; of later years it became more frontal. Constipation produced exacerbation, while correction of visual difficulties had been without influence. Some years previous to admission he had been told that there was a deficiency in the blood supply to the optic nerve. A few weeks before this consultation there had been an interval of several weeks during which he had experienced slight vertigo, uncertainty while walking, poor balance, and some slight speech difficulty.

*Family History:* There were several cases of cancer, probable pulmonary tuberculosis in a sister, and some cardiac disease. One sister also suffered from severe headache which was, however, apparently unassociated with the eyes.

*Past History:* Beyond the condition noted above he reported the usual minor ailments of childhood. At the age of 27 he had what was apparently an attack of appendicitis, followed by intervals of pain in the right lower quadrant and a tendency to constipation. Twenty years later the appendix was removed and at this time there was a lysis of adhesions which were quite extensive. Following this operation he had a three-day period of respite from headache which was entirely unique since the onset of the current complaint. At the age of 37 he developed pulmonary tuberculosis, which was pronounced arrested after six years' stay in Colorado. The patient had been married many years; his wife had borne four children with two miscarriages. Other facts in the history are a record of a slight trauma to the head in childhood, a moderate photophobia, frequent nosebleeds in childhood, and an infection of the right antrum, removal of a majority of his teeth, a tendency to infections of the respiratory tract, and slight hemorrhoids for many years. During the last few years the patient had been conscious

of a gradual slowing down of the mental processes, but this had failed to disturb his rather placid philosophy of life.

*Laboratory Summary:* The patient was a tall man, 12 per cent underweight and somewhat below his predicted lung volume. The basal rate was recorded as —15 per cent, a very moderate degree of hypofunction. With this was a low blood pressure and a definitely slow pulse. The urine showed both albumin and casts with a high residual nitrogen fraction. The sugar tolerance was normal, the blood chemistry normal, while the blood morphology showed a slight secondary anaemia with a substantially normal formula for the leucocyte count.

*Radiogram:* The teeth showed extensive periapical infection; the dorsal spine, hypertrophic arthritis; the skull was normal; the sella normal; optic canals unusually large but the bony margins were not eroded. The right frontal sinus was undeveloped.

*Chest Examination:* Dullness and some increased fremitus were observed. The condition was consistent with a healed tuberculosis.

*Laryngological Examination:* The examiner noted several doubtful teeth; infected but not apparently offending tonsils.

*Neurological Examination:* There was no direct evidence of organic nervous disease.

*Ear Examination:* No evidence of anatomical change.

*Barany Test:* Normal.

*Audiogram:* The hearing was fairly normal throughout the speech area coupled with a marked loss of hearing in the upper tones, suggestive of a luetic involvement of the 8th nerve.

*Surgical Examination:* Examination of the abdomen gave no evidence of tenderness or masses.

*Gastro-Intestinal Study by Roentgenogram:* Pericaecal adhesions were demonstrated.

*Eye Examination:* Showed marked cutting of the upper form and color fields, signifying pressure below the optic pathways, possibly in chiasm or possibly in the calcarine area. The blind spots were enlarged.

*Spinal Fluid Examination:* The results of this examination were negative except for a slightly high cell count.

*Discussion:* The laboratory picture here was not as sharply suggestive of thyroid failure as in some of the other illustrative cases. There was, however, a lowered basal rate which in a nervous individual would still be much above the truth. With this patient, however, there was a placidity arguing for probable authority in this test. The blood pressure and pulse were low; the kidneys gave some evidence of irritation. The urine volume was not suggestive. The high residual nitrogen and the normal sugar tolerance would be consistent with a thyroid failure. The supplementary tests, however, precluded such an interpretation of the laboratory findings.

CASE B-883—PULMONARY TUBERCULOSIS AND EPILEPSY SIMULATING HYPOTHYROIDISM. The patient's chief complaint was of convulsions from which he had suffered for the past five years. They were irregular in appearance, from twice in one day to once in two weeks, and lasted for periods varying from half a minute to ten minutes or more. The attacks also varied in severity, in the more severe of them there being frothing at the mouth, crying aloud and falling with loss of consciousness. There was apparently no aura and recovery was rapid after the passage of the seizure.

*Family History:* Not significant.

*Past History:* The boy reported only measles of the minor ailments of childhood and a broken left arm seven years previously. He reported infrequent headaches, an occasional nose-bleed, some nocturia, but the remaining history as given was practically without significant features.

*Physical Examination:* The patient was a well-developed, somewhat undernourished boy 13 years of age; the face and skin were pallid. The teeth were in good condition although they had received no attention. The lungs showed diminished tactile and vocal fremitus, but neither dulness nor rales were recorded. There was marked flat foot. The routine neurological findings were normal.

*Laboratory Summary:* The boy was 14 per cent underweight with a substantially normal lung volume. The basal rate was 20 per cent below prediction,

the blood pressure low, pulse normal, and there was a slightly febrile temperature. The urine volume was somewhat scanty and the excretion contained albumin. The nitrogen elimination indicated a wholly inadequate protein intake. The residual nitrogen fraction showed an upward tendency. The sugar tolerance was normal. The blood chemistry value was absolutely normal but in view of his very low protein intake the nitrogen constituents were relatively high.

*Chest Examination:* The left lung gave evidences of a probable active tuberculosis which indication was supported by the slight febrile temperature and other evidences.

*Röntgenogram:* Both lungs showed scattered, diffuse infiltration. The heart, mediastinum and skull were normal.

*Laryngological Examination:* Negative.

*Neurological Examination:* There were no objective neurological findings, the examiner regarding the history as suggestive of idiopathic epilepsy.

*Eye Examination:* Beyond yellowish discs and slightly enlarged blind spots, the results were normal.

*Discussion:* The laboratory picture here could have been interpreted in terms of thyroid failure had the other examinations and the history not indicated otherwise. The amyxedemic subject of thyroid failure is usually underweight. The boy was 20 per cent below his predicted basal rate with a slightly febrile temperature which could be interpreted as accounting for his pulse rate and in the correction of which a still lower basal value would be obtained. The boy's protein starvation is patently the cause of his low basal rate, however. The urine and blood picture were entirely consistent with the pseudo-nephritis of thyroid failure, while the lymphoid blood though not characteristic of this condition is to be expected in it. This case illustrates, in our opinion, the basic unwisdom of an effort to establish a diagnosis on the basal rate alone.

**CASE S-1057—PULMONARY TUBERCULOSIS REFERRED FOR HYPERTHYROIDISM.** The patient was a young man of 29 complaining of a lack of energy and ambition. He had been examined a month previously and told that this condition derived from thyroid disease and it was recommended that he receive treatment for this condition. The chief complaint had begun about two years previously and had been progressive during that interval.

*Family History:* The patient was a twin, his brother being in excellent health. The remaining family history was not relevant. The patient had been married for two years; his wife had borne one child, and had one miscarriage. The latter was ascribed to overwork.

*Past History:* The patient reported the minor ailments of childhood, scarlet fever, and a slight attack of pneumonia five years previously. He had been operated upon for a deviated septum a number of years earlier. He was subject to colds and a cough persisted after such an attack. Three years previously he had an attack of ptomaine poisoning and since that time he had been troubled with a mild gastritis and with flatulency.

*Physical Examination:* The patient was a well-developed but much undernourished young man of 29. The head showed a very prominent occipital protuberance suggesting a bony exostosis. The pupils showed a sluggish reaction to light and accommodation. The teeth gave evidence of much dental manipulation. The chest was flat, long and narrow, and there were marked supraclavicular depressions; rales were heard in both apices. The heart was normal; the skin dry and scaly; the knee jerks somewhat sluggish.

*Laboratory Summary:* The patient was 26 per cent underweight, lung volume slightly depressed. A satisfactory basal rate was 7 per cent above prediction; blood pressure was slightly low; pulse and temperature normal. The urine volume was somewhat large; remaining findings including the nitrogen partition measurements normal. The sugar tolerance was not determined. The blood chemistry was normal and the blood morphology presented a substantially normal picture.

*Röntgenogram:* The lungs showed increased prominence of the bronchial markings with peribronchial infiltration on both sides. A few small discrete calcifications were also noted.

*Discussion:* The interesting feature in this case is the normal basal rate coupled with the patient's definite emaciation. As will be noted in the table, the protein intake is ample. No part of the laboratory examination could be interpreted to support a diagnosis of thyroid failure, while the physical examination supported by the radiogram gave unmistakable evidence as to the cause of the patient's lassitude.

GROUP II. CASES SIMULATING SOME TYPE OF PITUITARY DISEASE

CASE S-1111—NORMAL INDIVIDUAL REFERRED FOR POSSIBLE HYPERPITUITARISM. The patient's chief complaint was of oversize, she being a young woman of 24 just under six feet in height. At about the age of 12 she began to grow very rapidly, and at the age of 14 developed a fatigability and fell behind in her school work from a lack of ambition and inability to study. Infrequently she had had severe generalized headache which, however, lasted for only a few hours. She reported an excessive appetite but stated that she maintained a fairly constant weight.

TABLE XIX  
Simulation of Pituitary Disease

	1	2	3	4	5	6
Case Number.....	S-1111	B-624	B-678	B-837	B-566	B-634
Sex.....	F	F	M	F	M	M
Age.....(yrs.)	24	39	41	57	61	59
Height.....(cm.)	179	160.5	178.5	159	167	173.5
Weight.....(kgm.)	72.6	61.4	62.9	81.8	76.2	73.4
Weight Deviation... .. (%)	-4	+11	-20	+25	+20	+20
Lung Volume Deviation... .. (%)	+1	-33	-17	-30	-31	-45
Basal Rate Deviation . . . (%)	-7	+20	-15	-2	-19	+38
Blood Pressure. . .(mm.)	112/71	130/80	102/58	192/108	110/78	264/120
Pulse Rate....(per min)	71	84	59	70	68	92
Temperature ... (deg.)	98.2	99.0	97.3	98.2	97.0	98.0
Alveolar CO <sub>2</sub> ... (mm.)	41	41	43	40	39	48
Urine Volume.. . .(cc)	1400	490	740	790	890	650
Spec. Grav.....	1.016	1.028	1.025	1.023	1.021	1.015
Albumin....	0	+	0	0	0	+
Casts.....	0	0	0	0	0	+
Sugar....	0	+	0	+	+	0
"Urobilinogen". .	0	0	0	0	0	0
Total Nitrogen... (gm.)	9.39	4.83	10.32	5.10	8.76	3.94
Residual Nitrogen. (gm.)	5.3	16.1	10.5	5.3	5.5	24.1
P. S. P. (2 hours) . (%)	7.5	46	32	54	47	0(?)
Galactose Tolerance						
Normal . . .(gm)		40	30	30	30	30
Observed ..(gm)		10	10	30	5	5
Deviation (%)		-75	-67	±0	-83	-83
Blood						
N. P. Nitrogen... (mgm)	33	30	30	35	43	47
Uric Acid (mgm)	3.0	4.7	3.1	3.2	3.4	5.4
Sugar (mgm)	96	105	87	95	100	105
Haemoglobin. (%)	85	95	80	85	90	55
Erythrocytes .. (10 <sup>6</sup> )	4.28	5.40	4.67	4.67	4.52	3.09
Color Index	1.00	0.88	0.86	0.91	1.00	0.89
Leukocytes (10 <sup>3</sup> )	5.1	7.6	8.8	7.6	7.8	7.2
Neutrophils. (%)	45	53	55	68	61	80
Lymphocytes (%)	50	40	36	21	35	9
Eosinophiles (%)	1	2	2	2	1	2
Endothelials (%)	4	4	7	9	3	9
Misc ... (%)	0	1	0	0	0	0
Wassermann.	0	0	0	0	+	0
Spinal Fluid .	0	0	—	—	—	—

- 1. Normal referred for Hyperpituitarism.
- 2. Paget's Disease simulating Hyperpituitarism
- 3. Cholecystitis and Duodenal Ulcer simulating Dyspituitarism
- 4. Cardiac with Roentgenogram of sella suggesting Pituitary Tumor.
- 5. Syphilis simulating Dyspituitarism.
- 6. Cardiorenal disease simulating Hyperpituitarism.

*Family History:* The patient's father was six feet in height. She had a sister 5 ft. 8 in. tall. The mother and a brother were of usual size.

*Past History:* The patient reported the usual ailments of childhood, diphtheria, and an appendectomy at the age of six. Beyond the points noted above the remaining history was entirely normal, including that of the catamenia.

*Physical Examination:* The patient was a very well-developed and well-nourished young woman with an exceptionally good musculature. There was a slight pilosity on the upper lip, and hypertrichosis of the extremities. The teeth

were apparently somewhat soft. The neck was large and muscular, the thyroid not palpable. The breasts were small but entirely normal. Remaining findings with the exception of hyperactive knee jerks were not significant.

*Laboratory Summary:* The patient was 4 per cent underweight; the basal rate 7 per cent below prediction. The urine was entirely normal. Blood chemistry was normal. Blood examination showed a slightly low value for the erythrocytes with a relative lymphocytosis.

*Roentgenogram:* The skull was normal; the sella of normal size and configuration.

*Eye Examination:* The blind spots were slightly enlarged.

*Discussion:* The patient's physical habitus was strongly suggestive of pituitary disease with overactivity of the anterior lobe. The laboratory examination completely failed to confirm this indication. It is, of course, possible that the patient had had an earlier period of pituitary overactivity but if such had been the case it had certainly been followed by spontaneous correction and at the time of the examination there was lacking any of the conventional evidences which experience has associated with disturbed pituitary function. The establishment of catamenia at the normal age, and its normal course thereafter, are arguments against the existence of any earlier significant disturbance of pituitary function. The girl was in a state of vigorous health, actively engaged in her profession. A study of this patient at some time in the future might be interesting from the standpoint of the present normal findings, but at present she illustrates the fallacy of making a diagnosis of an endocrinopathy from the history and physical examination alone. This case with those preceding it, prove the interdependence of complete clinical and laboratory examinations in the study of endocrine disturbances.

**CASE B-624—PAGET'S DISEASE SIMULATING HYPERPITUITARISM.** The patient's chief complaint was of pain in the right leg which she had first noticed some eight years previously. There was apparent improvement during the warm weather in the summer and an exacerbation in the winter, which in the last few years had become seriously crippling. Bandaging and rest had failed to bring relief. At the time of her periods of exacerbation there was usually intense headache and arthritic pains in the shoulders. During the previous year the attacks had become more frequent and of longer duration. A few months prior to admission a bony tumor had been removed from the right tibia. There had been a possible slight improvement as a result of this surgical intervention.

*Family History:* There was a definite history of longevity, the maternal grandfather having reached the age of 109.

*Past History:* In addition to the usual ailments of childhood the patient reported tonsillitis and four attacks of pneumonia. She had influenza at the time of the epidemic and had considerable pleurisy at this time with recurrences of the latter every winter. She had had repeated attacks of malaria prior to her attacks of influenza. She complained further of severe periodic headaches noted above which were accompanied by vertigo but which would ultimately be relieved by medication. During the attacks of pain there was a lowered aural acuity. She was subject to frequent head colds and had chronic catarrh. Had lost numerous teeth in connection with her several pregnancies. She complained of dyspnoea, palpitation, had had night sweats but not recently and an irritating but non-productive cough. She had occasional attacks of nausea in the morning. The menses were established at 12 and after a few periods amenorrhoea developed and persisted up to the age of 16 when the menses recurred spontaneously, the periods being of normal interval and amount. She had been married for 18 years and had borne four children without miscarriage. She reported herself as nervous, emotional and with a tendency to depression. A surprise would produce tingling sensations over the entire body and there was an intermittent numbness of the lower extremities with failure to apprehend sharp or dull point contacts.

*Physical Examination:* The patient was a well-developed, well-nourished woman of 40. There was a slight nasal obstruction, a coarse tremor of the tongue, many teeth missing, and the tonsils were enlarged. A blowing systolic murmur was reported and occasionally a diastolic murmur as well. The right leg showed residua of her earlier operation. The knee jerks were exaggerated, and on the right side she exhibited a crossed reflex of the adductor and flexor group of the left thigh.

*Laboratory Summary:* The patient was 11 per cent above her predicted weight and significantly below her predicted lung volume. The basal rate was

reported as 20 per cent above prediction and this finding was confirmed by later observations. The temperature was slightly high, the remaining physical findings, normal. The urine was scanty in volume and contained both albumin and sugar. The total nitrogen indicated an inadequate protein intake. The residual nitrogen fraction was much above the normal. The sugar tolerance showed a marked depression, confirming the record of glycosuria. The blood uric acid was distinctly above the normal. The blood morphology showed a lymphocytosis but was otherwise normal.

A report from the institution where the operation had been performed was as follows:

*"X-Ray Report:* There is an area extending from the mid-portion one inch below the lower end of the tibia which exhibits marked thickening of the cortex. The medulla is obscured in several areas while others of lessened density are observed in other portions." Later reports showed the condition apparently extending and some time thereafter an operation was performed exposing the point of greatest anterior convexity. The cortex of the tibia was found to be thick and dense, periosteum thin and adherent; irregular calcified areas were observed in the marrow cavity which when broken down formed a rough thin wall of the cavity. The bone tissue was soft as from a chronic degenerative process. No pus was obtained.

*Neurological Examination:* A positive Romberg test was reported, pupillary reflexes to light were stiff, the coordination of the upper extremities was very poor and there was a coarse tremor.

*Spinal Fluid:* Examination was entirely negative.

*Orthopedic Examination:* The leg condition was described and on the basis of the history, pathological findings at the time of operation, and general evidences, it was suggested that the condition was similar to that described by Henderson who named it an osteosclerosing osteitis.

*Roentgenogram:* The chest showed increased density over the lower half of both lungs; the skull showed thickening of the occipital and parietal bones with recalcification and sponge-like markings of the lateral wall. The pelvis, hips and lumbar spino showed calcium deposits of the bones with some increase in their transverse diameter. Similar changes were remarked in the lower half of the right humerus.

*Ear Examination:* There were some middle ear changes suggestive of early chronic catarrh.

*Barany:* Normal.

*Audiogram:* There was definite loss of hearing in both ears.

*Eye Examination:* The sluggish pupillary reflexes were not confirmed. Yellow discs, much enlarged blind spots, and marked symmetrical contraction of the form and color fields were noted.

*Discussion:* This patient had Paget's disease, with thickening of the skull, and probably some increase in intracranial pressure. Her scanty urine was not suggestive of pituitary disease. There was a high residual nitrogen, increased basal rate, high blood uric acid, much lowered sugar tolerance, and the findings of the eye examination were all suggestive of an overactive pituitary. It is perfectly true that intracranial pressure could have produced some disturbance of pituitary function; it would, however, be secondary to the presenting condition. There was seemingly some pulmonary involvement and one of us (A. W. R.) has already noted marked symmetrical contraction of the form and color fields in pulmonary tuberculosis. The intracranial pressure could produce a lowered sugar tolerance through interference with the central nervous system without involving the pituitary. It is to be noted that the blood sugar was entirely normal. The slightly increased basal rate was substantiated by two concordant measurements which were reported as satisfactory. In both of these, however, the pulse was somewhat rapid and at a level considerably superior to the daily pulse rate as shown by the nurse's record. While we feel that there may have been some secondary pituitary influence in this case, the bulk of the supporting evidences are susceptible of a non-endocrine explanation. The case is presented as an interesting simulation of pituitary disease which could have been misleading in the primary diagnosis. A later case, not recorded in this group, presenting Paget's disease in a much more advanced state, showed a like depression of the sugar tolerance and an entirely normal basal rate. This latter patient was much more stable nervously, and the basal rate probably more truly representative. It is interesting to note how purely extraneous factors may exercise an apparently constant influence on such a measurement as the basal rate. Elsewhere in these papers comment has been made on a case of paralysis



agitans with marked tremor which week after week showed a level which fell between the narrow limits of  $+60$  per cent and  $+65$  per cent. The true rate was either normal or possibly a little below, as was shown by certain supplementary measurements which need not be discussed here.

**CASE B-678—CHOLECYSTITIS AND DUODENAL ULCER SIMULATING PITUITARY DYSFUNCTION.** The patient's chief complaint was of flatulency and pain in the stomach associated with an intermittent diarrhoea. Four years previously he had a so-called nervous breakdown as the result of a strained domestic situation. On his recovery a few months later he began to experience pain in the lower left quadrant. He was examined and a varicocele was found which was operated and this relieved the pain in the left inguinal region. A few weeks later, however, he developed pain in the left lumbar, iliac, hypochondriac, and epigastric regions. The attacks of pain were intermittent but occurred periodically. At times food would relieve him, at others it was ineffective. Rest seemed to bring the greatest benefit. For the past three years he had had diarrhoea practically every summer. He was troubled with hemorrhoids; he emphasized the fact that there was no pain on the right side. He was of a high-strung nature, very nervous, and greatly disturbed if he were alone. He gave a long list of foods, mostly indigestible in character and with a high fat content, which he was unable to tolerate.

*Family History:* Not relevant. The patient had been married for a number of years but had divorced his wife at about the time of the onset of his present illness. The marriage had been infertile. The loss of his wife had affected him deeply and the unhappiness resulting from it was a very definite factor in the general picture.

*Past History:* He had no recollection of any of the minor ailments of childhood but had had an attack of melena at the age of twelve and many recurrences up to five years previously. He had had a number of teeth removed; complained of urinary frequency and urgency, during his periods of nervousness. The remaining history as given by him was not significant. As a matter of fact his physician had referred him for this study because of several transitory attacks of aphasia.

*Physical Examination:* The patient was a tall, thin man fairly well developed and nourished, 41 years of age. There was some loss of hair from the vertex, a suggested exophthalmos was no more than a family peculiarity, many teeth were missing, there was a doubtful thyroid enlargement. The breath had an odor which suggested to the examiner that of known gastric ulcer cases. The abdomen was apparently normal. There was a slight supraclavicular adenopathy, a contraction of the left side of the scrotum which was a post-operative condition, and a negative routine neurological examination.

*Laboratory Summary:* The patient was 20 per cent underweight and somewhat below his normal lung capacity. A basal rate of  $-15$  per cent was recorded with low blood pressure and a downward tendency to both pulse and temperature. The urine was somewhat scanty but otherwise normal. The residual nitrogen fraction was high. The sugar tolerance was depressed much below the normal level. The blood chemistry was normal. The blood morphology showed a slightly low haemoglobin value and a lymphoid blood.

*Surgical Examination:* Negative. In the examiner's opinion a peptic ulcer was probable.

*Radiograms of Gastro-Intestinal Tract:* The duodenum showed a niche on the anterior border suggesting a duodenal ulcer.

*Graham Test:* The test was negative but was performed by the oral route.

*Stool Examination:* The presence of blood was demonstrated.

*Eye Examination:* The pupils showed moderately active reactions and the fundi gave some evidence of vascular hypertension. The blind spots were enlarged and there was some contraction of the form and color fields.

*Discussion:* Were it not for the patent gastro-intestinal condition it would be possible in this case to consider a pituitary dysfunction as present. As it is, the lowered basal rate derives from the patient's under nutrition, the lowered sugar tolerance from the liver dysfunction which was offered in the preliminary opinion and later verified elsewhere, while the eye findings were also presumably referable to this latter cause.

**CASE B-837—CARDIAC DISEASE WITH A RADIOGRAM OF THE SELLA SUGGESTING PITUITARY TUMOR.** The patient's chief complaint was of severe headache local-

ized in the vertex and the occipital portions of the head. She also suffered from high blood pressure. Seven years previously at the time of the menopause, the patient being 50 years of age, she had developed very severe headaches, with which there was some associated vertigo. The hypertensive condition showed on examination and she was placed under treatment for this with a gradual improvement both in the blood pressure and in the headaches. Some eight months previously, however, there had been a recurrence of the condition and the physician called at that time recommended glandular therapy. Further questioning elicited the fact that five years previously she had had some trouble with her feet and her physician at that time recommended weight reduction and gave her thyroid therapy to produce this end. At other times she had been given other glandular preparations although she was not certain of the character of them. At the time of admission she had not been receiving any endocrine medication for several months.

*Family History:* Both mother and father had died of apoplexy and this fact intensified the patient's worry over her own high blood pressure. She had been married for 29 years without conceiving although contraception had not been practiced.

*Past History:* She reported minor ailments in childhood, pleurisy with effusion at the age of 14, abscessed tonsils at 15, and influenza at the time of the epidemic. Many years previously a herniotomy had been performed. At the time of admission she complained of a constant dull feeling of fullness in the head punctuated by very severe headaches as noted above. There had been a considerable loss of hair. She had two severe nose-bleeds five years previously; was subject to hay fever and apparently sensitized to a large number of pollens; she had had earlier sensitivity to strawberries which had corrected itself spontaneously. She had had three acute digestive attacks in the past three years characterized by nausea and vomiting. She had never been jaundiced but had had clay-colored stools after these attacks. She was somewhat constipated. Over 20 years earlier she had voided a small renal calculus after an illness of three days. There had been no recurrence. Menstrual history showed an early onset, large periods with shortened interval but from 1906 on until an uneventful menopause seven years previously, the function had been entirely normal. She regarded herself as nervous and emotionally unstable. She complained somewhat of vertigo.

*Physical Examination:* The patient was a well developed, obese woman 57 years of age; the hair was somewhat thin, peripheral vessels showed some degree of sclerosis, blood pressure was distinctly high, abdomen entirely normal, knee jerks hyperactive and the remaining routine neurological findings normal.

*Laboratory Summary:* The patient was recorded as 25 per cent overweight but with her high sitting height index this figure was actually too low. There was distinct though not severe loss of lung capacity. The basal rate was -2 per cent, blood pressure at a definitely hypertensive level, pulse and temperature normal. The urine volume was somewhat scanty; a slight trace of sugar was reported in the first specimen but could not be confirmed in subsequent examination. The protein intake was below a maintenance level; the partition formula was normal. The sugar tolerance was normal, blood chemistry normal, while the blood morphology showed an entirely normal picture.

*Roentgenograms:* The chest examination was negative. The skull showed a bony thickening of the inner table and there was apparently some erosion of the posterior clinoid process. The sinuses were negative. The plates of a gastrointestinal series were negative. The Graham test showed a normal organ.

*Laryngological Examination:* The patient had infected tonsils; the remaining examination was negative.

*Cardiogram:* Showed a left axis deviation consistent with, but not determining, cardiac enlargement. The remaining findings were entirely normal.

*Heart Examination:* There was a visible impulse in the suprasternal notch; definite angulation of the carotid arteries could not be detected on palpation; the heart was not enlarged; there was a soft systolic murmur with the first sound over the base and transmitted slightly toward the neck. The blood pressure was distinctly hypertensive. The examiner's opinion was of a chronic arterial hypertension without much change in the heart or the arteries.

*Orthopedic Examination:* The patient presented an obesity with a compensating lumbar lordosis. The posture was poor. Some of the joints of the hands showed a slight limitation in flexion due to a symptomless arthritis.

*Eye Examination:* The fundi gave evidence of a moderate degree of vascular sclerosis and there was slight blind spot enlargement.

*Neurological Examination:* No evidence of disease of the nervous system.

*Special Blood Examination:* The calcium, phosphorous and fibrin content was entirely normal.

*Discussion:* Stereoscopic plates of the sella were requested but it was not possible to secure them. In our experience we have had several reports of clinoid erosion which could not be substantiated at autopsy. In the present instance there was not one single finding suggestive of disturbed pituitary function. The normal basal rate would be as inconsistent with anterior lobe disturbance as would the normal sugar tolerance with that of the posterior. The single report of a trace of sugar in the urine could not be verified. With the condition of hypertension such as that presented by the patient such a glycosuria might well be referable to an injury to the central nervous system associated with arteriosclerosis. While the patient was obese, this fact alone would be a most uncertain basis for a pituitary diagnosis. It is, of course, always possible that there could be tumor growth of the pituitary without change of function. Such a condition in the thyroid is frequently remarked in endemic goiters. In our experience, however, cases presenting proven pituitary tumor have always given extensive and unmistakable evidences of disturbed pituitary function. In the present instance lacking every evidence but that of a flat x-ray plate we felt warranted in eliminating any pituitary element from the picture. The subsequent history of the case substantiated this conclusion. In view of the strictly non-endocrine character of this patient her earlier history of endocrine medication is not uninteresting.

**CASE B-566—SYPHILIS SIMULATING PITUITARY DYSFUNCTION.** The patient's chief complaint was of a marked fatigability complicated by pain in the left arm and shoulder, beneath the left breast, and at times in the left knee. This condition had obtained for the past six years. Over substantially the same period he had had more or less digestive disturbance and had been growing progressively more deaf. While active physically and strong muscularly, he had become more and more fatigable and for the past two years, as he phrased it, he had been working "on his nerve".

*Family History:* In the main not informative. Patient was married at the age of 21 and was divorced by his wife after 32 years of married life. During that period she bore three children without miscarriage. Four years previously he had married again. The second wife had never conceived.

*Past History:* He reported a few minor ailments, typhoid at 30, and diphtheria 10 years ago. Had always lived an active life and had worked very hard. He complained of a twitching of the right eyelid when tired; a gradual loss of hearing, more marked on the left side; a slight productive cough some years previously; a foul taste in the mouth on awakening; flatulency, and a variety of gastric disturbances which he could not describe clearly. At times he had a dull pain in the region of McBurney's point. He had had a Neisserian infection as a young man but denied lues. For a good many years he had had a left intercostal neuralgia and latterly some slight general swelling and stiffness in the joints. Also when fatigued there was a dull ache in the region of the sacrum.

*Physical Examination:* The patient was a well-developed, overnourished man of 61. The hair on the head was thin, the eyes apparently normal; there was a definite loss in aural acuity, marked varicoses on the under surface of the tongue. There was apparently a slight cardiac enlargement; the sounds were indistinct, but no murmurs were heard; the blood pressure was low. The abdomen was somewhat distended and there was apparently some flatness to percussion on the sides. There was moderate tenderness on deep palpation over McBurney's point and also some in the epigastric region. There was tenderness over the left shoulder at the acromio-clavicular junction, over the deltoid, and in the axilla; also on the medial aspect of the left knee. The hands showed some joint enlargement. Routine neurological examination was negative.

*Laboratory Summary:* The patient was 20 per cent overweight with definite loss of lung volume. The basal rate was recorded as —19 per cent; the blood pressure and temperature were low. The urine volume was a low normal; sugar was reported in all specimens. Residual nitrogen was normal, sugar tolerance greatly decreased. The non-protein nitrogen in the blood was above the normal; uric acid and sugar were normal. The blood morphology showed a slight lymphocytosis. The Wassermann and Kahn tests were repeatedly positive.

*Ear Examination:* Normal.

*Barany:* Normal.

*Stool Examination:* Negative.

*Cardiogram:* Normal.

*Heart Examination:* Beyond indistinct heart sounds, the heart was entirely normal.

*Neurological Examination:* The pupils showed sluggish reactions and there was an ill-defined tenderness over the nerves of the brachial plexus.

*Orthopedic Examination:* The case suggested sub-deltoid and sub-acromial bursitis. The left knee showed a slight degree of hypertrophic arthritis. There was also a suggestion of some abnormality of the semi-lunar cartilage.

*Abdominal Examination:* The findings reported in the physical examination were not confirmed. No surgical condition was demonstrated in the abdomen.

*Gastro-Intestinal Radiograms:* The stomach, duodenum, and bowel were normal. The appendix was diseased.

*Audiogram:* The curve showed that sharp loss in the upper tones which we regard as somewhat characteristic of syphilis.

*Eye Examination:* The pupillary reactions were sluggish, the remaining examination negative.

*Discussion:* While several independent disease conditions were demonstrated by this examination, those findings suggestive of a pituitary dysfunction would have been accounted for by the demonstrated syphilis. The opinion as to the underlying condition hinges about the serological examinations, and these gave positive responses on repeated testing.

**CASE B-634—CARDIO-RENAL DISEASE SIMULATING HYPERFUNCTION OF THE PITUITARY.** The patient's chief complaint was of marked distress and shortness of breath. This condition had appeared in recurrent attacks of several weeks' duration, the first of which was remarked three years ago. During the lapse of time they had occurred more frequently and in the past few months the dyspnoea had been practically constant. He had acute attacks of shortness of breath which would wake him up at night. Treatment with nitro-glycerine had been non-effective. There was also a progressive weakness of the skeletal muscles without abrupt loss of control or paralysis.

*Family History:* Negative.

*Past History:* The patient reported the minor ailments of childhood and a hemorrhage of the stomach at the age of 27. He complained of occasional headaches, some vertigo, a non-productive cough, an occasional night sweat which he ascribed to nervousness, and a normal gastro-intestinal history. He stated that the urine stream was slow in starting and subject to interruption. There was some dysuria of varying degrees. The prostate had been examined a year or two earlier and pronounced normal. He had gonorrhea twice in young manhood and syphilis at about the same time. Was treated for the latter with apparent success as numerous Wassermann tests have always been negative. He complained of intermittent pain in various joints which was never accompanied by swelling. He had at one time been very obese but had gradually lost nearly 100 lbs. during the past 20 years.

*Physical Examination:* The patient was a well-developed, overnourished man of 59 years of age. There were numerous small unpigmented papillomata on the face. The pupillary reactions were somewhat sluggish. The nose suggested rhinophyma. The expirations were prolonged and marked friction rubs were heard throughout the chest. There was a slight dulness in the upper chest, tactile and vocal fremitus increased in the right apex, and many dry coarse rales were heard throughout the chest. The heart was enlarged to percussion and there was a systolic murmur at the apex. The abdomen was asymmetrical, the left abdomen being somewhat enlarged. There was some flatness on percussion; the liver was apparently enlarged. A cough impulse was felt in the left inguinal region. There was some edema of ankles and feet. The routine neurological examination was negative.

*Laboratory Summary:* The patient was 20 per cent overweight and definitely below his predicted lung volume. The basal rate was reported as 38 per cent above prediction. There was a marked degree of hypertension with somewhat rapid pulse. The urine volume was somewhat low; albumin, granular and renal cell casts were observed. The protein intake was entirely inadequate; the residual nitrogen fraction was definitely high. Three repeated sulphoph-

thalein tests failed to return enough of the dye to measure quantitatively. The sugar tolerance was greatly diminished; both non-protein and uric acid were much above the normal; the blood morphology showed a marked secondary anaemia and a predominance of the neutrophilic elements.

*Röntgenograms:* The skull was normal. A measured heart plate showed definite cardiac enlargement. There was a diffuse mottled infiltration of both lungs, more marked at the bases.

*Cardiogram:* There was a left axis deviation consistent with cardiac enlargement. The initial ventricular complex was of maximum duration and, together with the inversion of the "T" waves, indicated a probable impairment of the ventricular myocardium.

*Discussion:* The patient was an advanced case of cardio-renal disease with the possible complication of a neuro-syphilis which it was felt wiser not to investigate by spinal puncture. The increased basal rate could derive from the patient's breathing and the inability to secure a truly basal reading. The high residual nitrogen of the urine is no more than an evidence of this toxic state. The high blood uric acid is robbed of its endocrine significance by the high values of the other nitrogenous constituents. The low sugar tolerance is referable either to the arterio-sclerosis, the possible neuro-syphilis, or a possible liver condition suggested by the report of hepatic enlargement. In the same way other suggestions of possible endocrine disorder are directly traceable to the better established non-endocrine conditions which presented. This laboratory picture is a simulation of a hyperpituitary state for which supporting evidence is entirely lacking.

### GROUP III. CONDITIONS FREQUENTLY ASCRIBED TO ENDOCRINE CAUSES.

**CASE S-1712—DELAYED ONSET OF MENSTRUATION DUE TO PULMONARY TUBERCULOSIS.** The patient's chief complaint was of having failed to establish the menses at the age of 18. She had been under medication for this condition for some time and complained of periodic attacks of pain, occurring at intervals of four weeks and lasting for one day. These pains had developed since beginning her medication. She also complained of marked fatigability.

*Family History:* Negative.

*Past History:* In addition to the minor ailments of childhood the patient had a severe attack of influenza at the time of the epidemic and had been consistently susceptible to respiratory infections. She reported the loss of 20 lbs. in the past 2 years. She had had frontal headaches but these had been corrected by proper glasses. She complained further of indigestion after eating fried foods. The remaining history as given was entirely irrelevant.

*Physical Examination:* The patient was a well-developed and well-nourished young woman nearly 19 years of age. There was some tonsillar enlargement, rapid pulse rate, a loud systolic blowing murmur most marked at the apex and transmitted to axilla and sternum. The remaining findings were normal. It should be noted in passing that an incompetent examiner failed to note the definite evidences of pulmonary disease.

*Laboratory Summary:* The patient was 6 per cent overweight but as the sitting height index was low this figure is misleading and she was actually somewhat underweight. The lung volume was much below the predicted level. The basal rate was normal. She had rapid pulse, low blood pressure and slightly sub-normal temperature. Beyond a slightly low volume and a definitely high residual nitrogen, the urine picture was substantially normal. The sugar tolerance was not determined. The blood uric acid was high. The blood was lymphoid in type.

*Pelvic Examination:* Entirely negative.

*Laryngological Examination:* Tonsils were buried, cryptic and infected. There was some muco-purulent material in both nares.

*Radiogram:* Both lungs were hazy. There was increased density of the whole of the right lung, fine linear markings of fibrosis and scattered mottled areas.

*Cardiogram:* This indicated a normal mechanism at an accelerated rate.

*Eye Examination:* Slight blind spot enlargement.

*Discussion:* The medicine used in this case was said to be a preparation of wormwood. The patient had a definite pulmonary tuberculosis, confirmed by later examination. There was no evidence in the laboratory examination of any

TABLE XX  
Conditions Ascribed to an Endocrine Etiology

Case Number		1	2	3	4	5	6	7
		S-1712	S-131	B-356	B-123	B-663	B-251	B-339
Sex		F	M	F	M	M	F	M
Age	(yrs)	18	52	16	24	7	22	5
Height	(cm)	165 0	193 0	143 5	157 5	99 0	151 0	103 0
Weight	(kgm)	53 0	145 0	40 0	52 4	19 3	40 5	15 5
Weight Deviation	(%)	+6	+67	-7	-12	-15	-1	-10
Lung Volume Deviation	(%)	-44	-23	-11	-8	-24	-20	-16
Basal Rate Deviation	(%)	-1	+6	-10	+7	*+22	-3	+7
Blood Pressure	(mm)	106/64	156/78	94/58	92/58	88/68	118/84	95/52
Pulse Rate	(per min)	106	76	72	71	100	81	90
Temperature	(deg)	97 4	97 8	98 6	98 8	99 2	98 8	97 8
Alveolar CO <sub>2</sub>	(mm)	41	52	33	36	42	29	35
Urine Volume	(cc)	780	1540	1150	920	330	460	960
Spec Grav		1 021	1 021	1 012	1 027	1 030	1 021	1 013
Albumin		0	0	+	0	0	+	+
Casts		0	0	+	0	0	0	0
Sugar		0	0	0	+	+	+	0
"Urobilinogen"		0	0	0	0	0	0	0
Total Nitrogen	(gm)	8 55	11 46	7 75	15 38	5 12	4 70	5 38
Residual Nitrogen	(%)	15 3	8 7	8 1	3 0	21 6	6 7	7 9
P S P (2 hours)	(%)	54	61	64	48	53	57	51
Galactose Tolerance								
Normal	(gm)			40	30	30	40	30
Observed	(gm)			20	40	5	40	20
Deviation	(%)			-50	+33	-83	± 0	-33
Blood								
N P Nitrogen	(mgm)	30	35	33	40	25	31	30
Uric Acid	(mgm)	4 2	4 5	3 0	4 4	2 8	2 5	2 8
Sugar	(mgm)	95	109	96	83	80	81	*117
Haemoglobin	(%)	90	100	100	100	80	75	85
Erythrocytes	(10 <sup>6</sup> )	4 98	5 67	5 80	5 55	4 26	4 16	4 87
Color Index		0 90	0 88	0 86	0 90	0 94	0 90	0 87
Leukocytes	(10 <sup>3</sup> )	6 9	7 65	5 40	7 70	10 2	7 7	10 0
Neutrophiles	(%)	56	40	54	68	42	62	39
Lymphocytes	(%)	35	43	39	24	47	29	37
Eosinophiles	(%)	2	6	4	0	6	5	6
Endothelials	(%)	6	9	3	7	5	4	18
Misc	(%)	1	2	0	1	0	0	0
Wassermann		0	0	0	+	0	0	0
Spinal Fluid		—	—	—	—	—	—	—

\*Too high emotional reaction

- 1 Delayed menstrual onset due to pulmonary tuberculosis.
- 2 Obese Normal Giant simulating Hypopituitarism
- 3 Dwarfism with congenital Syphilis
- 4 Chondrodysplasia with syphilis (congenital)
- 5 Achondroplastic dwarf with rickets and congenital malformation of skull and spine producing a lesion of the central nervous system
- 6 Progressive muscular dystrophy
- 7 Diabetes insipidus

endocrinopathy. The delayed onset of the menses must be ascribed to the asthenia deriving from the pulmonary condition. The administration of an endocrine preparation containing thyroid extract to a patient with active tuberculosis is of course definitely contraindicated, yet such therapy is recommended as a "therapeutic test" in amenorrhoea by certain contributors to "endocrine" literature.

**CASE S-131—AN OBESE, NORMAL GIANT, SIMULATING PITUITARY DISEASE.** The patient had no chief complaint other than obesity which dated back to early childhood and which had always been correctible by dietary measures.

**Family History:** The family history showed an unusual degree of longevity in the previous generations; the whole family was composed of large, heavy individuals. The patient had been married for 10 years but the union was infertile.

**Past History:** The patient reported only measles in childhood, a peritonillar abscess 12 years previously, and a brief attack of arthritis 6 years earlier. The remaining points were a tendency to constipation, occasional distress after eating and rarely, an attack of lumbar pain. The whole history was in the main one of vigorous health.

*Physical Examination:* The patient was a man of large stature weighing over 300 lbs. Development was excellent and there was marked physical strength and muscular development. The pupillary reactions were slightly slow; several teeth were missing but the remainder were in excellent condition. The blood pressure was slightly high. Knee jerks were somewhat sluggish. Remaining examination was not significant.

*Laboratory Summary:* The volume of the urine was normal, and the material itself free from abnormality. The patient was 67 per cent above his predicted weight and somewhat below his predicted lung volume. The basal rate was +6 per cent; the blood pressure, as noted, slightly high; pulse and temperature, normal. The sugar tolerance was not determined. Blood chemistry was normal except for a high uric acid. Blood morphology was normal except for lymphocytosis and 6 per cent eosinophilia.

*Neurological Examination:* Entirely negative.

*Radiographic Examination:* The skull, sella, and sinuses were normal.

*Cardiogram:* Normal.

*Audiogram:* Normal.

*Laryngological Examination:* Negative.

*Eye Examination:* The fundi showed slight vascular sclerosis and there was a very slight blind spot enlargement.

*Discussion:* On outward evidences this patient would have been diagnosed as a case of pituitary disease and the obesity considered to be probably of that origin. The only two points which could support such a diagnosis were the high blood uric acid and the eosinophilia; in addition there was the general though not specific indication of a lymphoid blood. That there may have been an earlier pituitary condition is certainly possible, but at the time of this study there were no valid evidences to support a diagnosis of current pituitary disease. Subsequently by moderate dietary restriction alone the patient took off some 60 lbs. in weight. The case is presented as records show that many subjects of obesity who presented far less convincing outward evidence of pituitary disease have been given pituitary medication for its correction.

**CASE B-356—DWARFISM WITH CONGENITAL SYPHILIS.** The patient's chief complaint was of small stature, she being but four feet nine inches tall at the age of 16.

*Family History:* The child was illegitimate; the father was unknown and the antecedents of the mother not a matter of record.

*Past History:* The patient reported none of the minor ailments of childhood but had a history of frequent sore throats, which had recently been somewhat benefited by a tonsil operation. She had had severe left frontal headaches all her life, at times accompanied by nausea and by occasional vomiting. The eyes were astigmatic and not strong. She complained of occasional vertigo and had had several fainting attacks after moderate exercise. She complained also of tinnitus which usually accompanied her vertigo. She had established the catamenia some six months earlier and the periods have occurred at intervals of from two to three weeks. They were apparently normal in duration and amount. There had been no increase in her weight or height for eighteen months prior to admission.

*Physical Examination:* The child was well developed, if allowance be made for her small stature. She was in an excellent state of nutritional equilibrium. The hair was abundant and coarse, with both light and dark strands and a few streaks of gray; a rather heavy growth in the axillae and on the pubis, the latter being normal in distribution. The pupillary reactions were very sluggish. The teeth were small and very closely set. The breasts showed inverted nipples. The heart and lungs were apparently normal. The routine neurological findings as reported were apparently normal.

*Laboratory Summary:* The child was 7 per cent below her predicted weight, but as the sitting height index was somewhat high, she was actually somewhat nearer conventional standard. The lung volume was but slightly increased. The basal rate was -10 per cent, this being the lowest value of several concordant determinations. The blood pressure was low. The value obtained for alveolar carbon dioxide was low, but this was probably due to the difficulty in obtaining a truly representative sample. The urine volume was normal; both albumin and casts were reported. The protein intake was adequate but not liberal. The residual nitrogen fraction was within normal limits. The sugar tolerance was half

the normal. The blood chemistry was normal. The blood showed a lymphoid trend with a 4 per cent eosinophilia.

*Neurological Examination:* Negative.

*Radiographic Examination:* The skull was normal, as was the heart; there was some increased density over the pulmonary apices.

*Eye Examination:* The eyes showed the pepper and salt pigmentation of the retinae characteristic of congenital syphilis. As already noted, the pupillary reactions were sluggish; there was some loss of visual acuity. Both form and color fields were symmetrically contracted in moderate degree and the blind spots were definitely enlarged.

*Discussion:* There was nothing in this case to indicate any endocrine cause of her dwarfism. The social history, lowered sugar tolerance, and the very characteristic eye findings were felt to indicate the probable cause of the patient's arrest. We were unable to secure permission to perform a lumbar puncture. The Wassermann on the blood was negative, which fact naturally would not invalidate the conclusion reached above. There was a report which we could not confirm that the mother was known to have been syphilitic. What was known of her social history, however, made the report a very credible one.

**CASE B-123—CHONDRODYSPLASIA WITH CONGENITAL SYPHILIS.** The patient was a man of 24 presenting as his chief complaint an inability to pronate the right forearm. There were numerous exostoses on all of the long bones. The difficulty with the forearm apparently originated after a fall in which he injured it. The generalized exostoses, so far as he knew, went back to early childhood.

*Family History:* At the time of his admission he reported only the death of his mother from tuberculosis, and an arthritic condition in his father. Later when the study was well under way in response to indirect questioning he added that the father was a man of very loose sexual life and that to his knowledge he had been under treatment for venereal disease.

*Past History:* The patient had apparently escaped all of the minor ailments of childhood, scarlet fever at the age of 9, and the removal of a wen some years earlier being the only two incidents noted. He denied venereal disease by name and symptom. His remaining history was substantially irrelevant.

*Physical Examination:* The patient showed fair development and nourishment. The teeth gave evidence of much dental attention. There was a slight enlargement of the thyroid; the ribs were prominent and beaded; the heart was apparently normal; the liver was slightly enlarged but was not tender and there was no tenderness over the gall bladder region. There was limited pronation of the right forearm, but no limitation of motion. Marked exostoses could be demonstrated at both the upper and lower ends of all of the long bones. This condition was most pronounced at the lower ends of the femurs and tibiae. Over-riding toes presented on both feet. The skin showed a generalized acne. The remaining findings were not remarkable.

*Laboratory Summary:* The patient was 12 per cent below his predicted weight but as he had the very high sitting height index (0.555), the predicted weight was disproportionately high. The lung volume was practically normal. The basal rate showed the normal value of +7 per cent, the blood pressure was definitely low. Alveolar carbon dioxide was a low normal. The urine volume was normal, elimination good; a trace of sugar was recorded. The protein intake was ample—the patient spoke of himself as a very large meat eater. The partition formula was normal. His sugar tolerance was reported as slightly above the normal. This finding was regarded as questionable since he eliminated nearly two grams with a test meal of 40. The patient was not entirely cooperative and it was impossible to verify this finding by repetition. On the basis, however, of many thousands of these tests, it was felt probable that his sugar tolerance is either normal or even possibly diminished. The record, however, is given as it stands. It will be noted there was a slight glycosuria. The blood uric acid was above the normal but the non-protein nitrogen was at a similar high level. The blood morphology showed a substantially normal picture. The Wassermann test gave a strongly positive response in several independent observations.

*Eye Examination:* The pupillary reactions were sluggish. The form fields were normal, the color fields distinctly contracted, the left being more pronounced than the right. There seemed to be some lack of clearness in the media so that the fundi were seen only hazily. The interpretation was of choroidal involvement of possibly specific origin.



*Barany Test:* The patient showed normally functioning labyrinths.

*Radiographic Examination:* The skull and sella were normal. The long bones showed a profusion of exostotic processes.

*Discussion:* The patient presented a clear-cut case of hereditary, deforming chondrodysplasia. There was no evidence anywhere in the examination of any endocrine involvement, the slight thyroid enlargement observed in the physical examination being no more than a slight hyperplasia without toxic features. There was a clear-cut syphilitic condition verified beyond any possible doubt, and this seemed to be congenital in origin although naturally its presence through acquirement could not be ruled out.

**CASE B-663—AN ACHONDROPLASTIC DWARF WITH RICKETS AND A CONGENITAL MALFORMATION OF THE SKULL (HYDROCEPHALUS) PRODUCING A LESION OF THE CENTRAL NERVOUS SYSTEM.** The patient was a six-year-old boy less than 100 cm. tall, presenting a disproportionately large head. He had been a full-term child, normally delivered, but the large head was noted at birth. He was a very sickly baby for the first two years of his life, and during the first year he had an attack of vomiting after each nursing which continued for a period of about two weeks. The head was very heavy and up to the age of one year always had to be supported. At the age of 2 light therapy was applied to the spine without any change in the condition. At this time, in the mother's words, the head seemed almost larger than the body. As he approached his third year he began to improve spontaneously. The body has grown but the head remained still disproportionately large. During the last year or two he has been able to play with other children and has even entered kindergarten. He presented some speech difficulties. The ears had discharged and there had been a loss of aural acuity. He has always complained of undue fatigability.

*Family History:* The parents were living and well and there were two normal siblings. The remaining family history was irrelevant.

*Past History:* The patient had all of the minor ailments and had always been subject to very severe colds. As noted above, there had been loss of hearing and an intermittent discharge from the ears. The child had always been a mouth breather and there were other evidences of possible partial obstruction. The teeth were very soft and decayed easily. At times the child had had night sweats. The remaining history did not depart materially from the normal.

*Physical Examination:* The patient presented the appearance of a child with the form of an aged man and with a distinctly large head. There was no suggestion of a progeria as this term is usually understood. There was very poor posture, marked lordosis, knock-knee, and bowed tibiae. The head was symmetrical, prominent in the frontal parietal regions making the occiput large in comparison with the face. The sutures and fontanelles were closed but marked by depressions. The facial expression was dull. The teeth were in very poor dental repair, the incisors presenting saw-tooth edges. The palate was high and arched, the tonsils large and cryptic. A rosary was noted but there was no Harrison's groove. An occasional squeaky rale was reported. There was distinct tachycardia. The abdomen was bulging with marked ptosis, but was otherwise normal. The epiphyses at the knees were markedly enlarged, the right shoulder drooped, and there was a marked dorso-lumbar lordosis. There was some degree of mental retardation. Articulation was indistinct. Biceps, radial and knee jerks were sluggish.

*Laboratory Summary:* The boy had a very high sitting height index in part, at least, due to the leg deformity. He was 15 per cent below his predicted weight and definitely below his predicted lung volume. It was impossible to get a satisfactory basal rate. The most dependable gave a value of 22 per cent above the more reliable standards. The blood pressure was low, the pulse showed an upward tendency, the temperature was slightly febrile. There was no question that the rate as recorded was significantly above the truth. The urine volume was scanty, elimination fair; a trace of sugar was reported. His protein intake was adequate but not liberal; the residual fraction showed a very high value. The sugar tolerance was greatly depressed; in fact a few grams of galactose would invariably produce a positive test. The blood chemistry was normal and the blood sugar at the low normal level. The blood showed a slight secondary anaemia, a lymphocytosis presumably influenced by the patient's age, and a 6 per cent eosinophilia.

*Ear Examination:* The patient showed chronic discharging ears.

*Neurological Examination:* There was a moderate hydrocephalus. No signs of organic nervous disease were elicited. The patient seemed a little less alert than the average child of his age.

*Laryngological Examination:* Tonsils were markedly enlarged, cryptic, and infected.

*Orthopedic Examination:* This confirmed the earlier indications of rachitis.

*Audiogram:* There was a definite loss of hearing in both ears.

*Radiographic Examination:* The skull was of the hydrocephalic type with convolutional impressions on the inner table and prominent diploic veins. The sella was normal; the chest was normal; all of the long bones showed deformities of maldevelopment. There were wide epiphyseal spaces between the ilium and ischium.

*Eye Examination:* The fundi showed tortuous vessels. There was a symmetrical contraction of the form and color fields to less than 10 degrees, precluding the delineation of the blind spots.

*Discussion:* The child patently had a congenital hydrocephalus, and superimposed upon this was a rachitis. The test gave no evidence whatsoever of any endocrine involvement, all of the departures from the normal being patently referable to demonstrated non-endocrine conditions. It is interesting to note that a complete check-up determination made one year later, confirmed all of the findings here presented, and in addition gave a basal rate at a somewhat lower level than that recorded above. The lack of definition of standards in children of this age forbids too exact an interpretation. Our measurements, however, would seem to indicate that the boy's oxygen consumption was probably within the normal range.

**CASE B-251—PROGRESSIVE MUSCULAR DYSTROPHY.** This condition is one which is frequently assumed to derive from an endocrinopathy. The present report, drawn from one of our cases, is typical of the members of the small group which we have examined, none of whom have given evidence of any present or past endocrine disease.

The patient was a 22-year-old girl, complaining of difficulty in moving both arms coupled with pain in the left knee. She was also extremely nervous. Some two years previously she had first noticed an undue fatigue at the end of the day's work. The condition had rapidly progressed and in a short time her night's sleep produced no refreshment. Rest was advised for the condition, but was without benefit. Some eighteen months previously the condition was complicated by the development of a pain factor which at first was generalized in character but later localized in the shoulder and then radiated downward through the arms. She also noted a progressive loss of strength in the right hand and arm which at times seemed heavy and numb. Later, she noted that the muscles of the hand were atrophying, those of the palm being first involved, while later, the thenar and hypothenar eminences began to disappear. The muscle wasting had gradually progressed to involve the fore- and upper-arms. During the month prior to admission pain in the left knee had become a factor.

*Family History:* Her mother had had a successful removal of a breast cancer 15 years previously. The remaining history was negative. The patient was unmarried.

*Past History:* She reported the usual minor ailments of childhood, an appendix operation seven years previously, and a nervous breakdown two years before admission. Eight years earlier or six years before the onset of her present condition the patient had scalded her right arm and shoulder. She complained of loss of visual acuity, an occasional severe earache, a susceptibility to head colds, sore-throats and tonsillitis. She experienced dyspnoea on slight exertion. At times was nauseated but not to the point of vomiting. The catamenial history was initially normal with onset at the age of 14, and an uneventful course up to two years previously. At that time there was a brief period of shortening of the intermenstrual interval with spontaneous restoration to normal rhythm within a few months. The patient had lost 34 lbs. in the past two years. During the course of the present complaint she had had occasional attacks of vertigo and had developed a definite emotional instability.

*Physical Examination:* The patient was a poorly developed, and nourished woman of 24. The pupils were dilated and the reactions were sluggish. The teeth gave evidence of much dental attention. The heart and lungs were normal as was the abdomen. The right arm showed slight wasting of the muscles of the upper arm and marked wasting of the forearm. There was also marked wasting of the interossei, more particularly on the palmar surface. There was

an absence of the thenar and hypothernar eminences, continual flexion of the fourth and fifth fingers and permanent extension of the first finger. Only the second finger showed free motion. The patient was unable to raise her forearm and hand to the face but achieved this by action of shoulder and arm muscle. The left arm showed free motion but moderate wasting in the palm of the hand and of the thenar eminence. The legs were apparently not wasting but there was tenderness in the popliteal space; also a marked tenderness along the course of all nerves of the hands and arms. There was also tenderness along the ganglia of the 7th and 8th cervical, the first two thoracic and the lumbar nerves. The abdominal reflexes and knee jerks were exaggerated.

*Laboratory Summary:* The patient was recorded as but 1 per cent underweight, but with her low sitting height index this was less than the truth. There was slight but definite loss of lung volume. The basal rate was normal as were the associated physical findings. The low alveolar carbon dioxide resulted from the inability to collect a representative specimen. The urine volume was scanty, elimination was poor. Both albumin and sugar were noted. The protein intake was inadequate. The nitrogen partition formula was normal. The sugar tolerance was normal. The blood chemistry was normal. She had a secondary anaemia and a 5 per cent eosinophilia.

*Radiographic Examination:* The skull, sella, cervical and lumbar spine, pelvis, and chest were all normal. She showed one infected tooth.

*Barany Test:* The labyrinth function was normal.

*Eye Examination:* The pupillary reactions were very stiff; the discs were chalk white; the fields could not be exactly delineated but were definitely concentrically contracted. In the examiner's opinion there was evidence of a secondary atrophy with the lesion at or behind the chiasm.

*Discussion:* The examination of this case was incomplete as the result of conditions outside of our control. It is quoted, as stated above, solely to demonstrate the complete absence of any indication of endocrine disease, and as also noted above, the findings here are typical of other cases which we have had opportunity to study.

**CASE B-839—REFERRED FOR DIABETES INSIPIDUS.** The patient was a 5-year-old boy whose chief complaint was reported as polydipsia, polyuria, and nocturnal enuresis. Up to the age of three the child had been apparently normal. At this time he had an attack of measles, and subsequent to this he had wet the bed once or twice every night. Treatment at the time of onset was not effective and attempts at curtailing his fluid intake in the late afternoon had been abortive as the child would cry and the mother would give him liquids. During the preceding summer the mother noted that the child was continuously thirsty, that he drank very frequently and passed large quantities of pale urine. Three months before admission he developed acute abdominal pain and passed into a state of coma in which he remained for three days. She informed us the condition was due to "acidosis" but added that the child had previously eaten berries in one of the public parks that had recently been sprayed with arsenate of lead.

*Family History:* The patient had five siblings none of whom exhibited his difficulty. The remaining history was negative.

*Past History:* The child was a full-term, instrumentally delivered baby, breast fed for three months, and then on a variety of artificial preparations which produced a transitory attack of eczema. The child had measles and whooping cough and the condition noted above at the age of 5. He complained of an occasional headache, was subject to head colds and had recurrent attacks of eczema. During the past year there had been periods when the child would wake at night and complain of pain in the calf of the right leg. Massage would speedily stop this.

*Physical Examination:* The patient was a poorly developed and nourished child, of apparently normal intelligence. There were numerous eczematous lesions on the face, back and arms. The bridge of the nose was somewhat depressed but there was no apparent obstruction. The tonsils were large and red-dened. There was a distinct cervical adenopathy. The boy's posture was bad with a moderate degree of lordosis. The remaining findings were normal.

*Laboratory Summary:* The boy was 10 per cent underweight with a slightly depressed lung volume. A fairly dependable basal rate was within normal limits. The urine volume, while ample for a child of this age, did not confirm the report of a marked polyuria. Albumin was present. The nitrogen partition was normal. The sugar tolerance was slightly low. Blood chemistry was normal, the

slightly high blood sugar undoubtedly deriving from the patient's emotional response to venipuncture. The blood morphology showed an increase in both the eosinophiles and the endothelial leucocytes.

*Skin Examination:* The condition was defined as eczema of the erythematous-squamous type.

*Neurological Examination:* Normal.

*Orthopedic Examination:* Normal.

*Chest Examination:* Normal.

*Abdominal Examination:* Normal.

*Nose and Throat Examination:* Normal.

*Eye Examination:* Incomplete but so far as obtainable, normal.

*Discussion:* It was impossible to secure x-ray pictures of this child as he was very restless during the first attempts and the mother would not give her consent to a repetition. The only real departure from the normal which the child presented was the slightly depressed sugar tolerance. This could well arise from a variety of causes, and there was nothing in the remaining examination to imply an endocrine significance to it. We do not regard this case as one of proven diabetes insipidus although the verbal report of the referring physician indicated that there had been times in the child's life when the urine output was much more suggestive than at the time of our study. There was certainly no evidence here of any pituitary involvement. The case is offered as one in which endocrine medication might well have been exhibited on the basis of the putative history and yet which on examination failed to offer any evidence to warrant such a procedure.

It will be noted that in the preceding protocols little or no reference is made to treatment. The immediate concern of these studies has been the diagnosis of endocrine disorders, and the response of the patient to endocrine therapy has constituted a therapeutic test offering some measure of support to the accuracy of the diagnostic conclusion. In the present series of cases the diagnostic interest rests upon the fact that the patients simulate or suggest endocrine disease, but demonstrate on analysis a non-endocrine etiology for their presenting condition. The treatment of this numerous group of non-endocrine disorders would follow the conventional lines of current practice and consequently is not germane to our thesis.

Before bringing this article to a conclusion the authors wish to stress the implications of the present paper. That a patient presents outward evidences of, or symptoms suggesting, an existing endocrinopathy, does not in any way prove the existence of such a state, nor does it serve as a warrant for the exhibition of endocrine preparations therapeutically. This latter practice followed empirically and without the warrant of an established diagnosis, at the best can only prove abortive in correcting the patient's difficulty, and at the worst may do grave and serious damage to a diseased organism. It should be hardly necessary to repeat this caution, and yet a large number of patients referred to us who report in their histories the administration of powerful glandular products without other warrant than an uncritical expectancy, indicate the urgency. Endocrinology is a field in medicine in which great benefit may be wrought by the correct use of its powerful therapeutic agents and even greater damage done by their misuse.

# MALIGNANT ADENOMA OF THE PARATHYROID GLANDS\*

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Knowledge of parathyroid tumors is rather recent. Sandström suggested the hypothesis of their origin when he discovered the parathyroid gland in 1880. According to Bérard and Alamartine, parathyroid tumors were for a long time difficult to distinguish from tumors of the thyroid gland, and many were diagnosed as fetal adenomas of Wolfer. Kocher, in 1899, described five cases of goiter containing glycogen and suggested that they might be parathyroid glands. In 1900, De Santi first described a parathyroid tumor in the carotid region. Some of the tumors did not cause symptoms during life and were discovered at necropsy. Small nodules were found in the usual parathyroid situation or deeply placed in the thyroid gland and encapsulated.

It is known that parathyroid glands are found in various situations and that they might give rise to hyperplasia and even tumors, just as accessory thyroid glands and accessory breast tissue give rise to carcinoma.

There seems to be some relation between extensive destruction of bone, and parathyroid tumors and hyperplasia. Erdheim (7) found tumors in six cases of osteomalacia, which has been extended by others to occur in osteofibrosis and osteoporosis. Some authors interpret hyperplasia as a functional activity tending to compensate for disturbed calcium metabolism.

Kerl reported a case of extreme osteomalacia and one case of osteoporosis, in each of which the parathyroid glands were markedly hyperplastic, but lesions were not found in any other endocrine gland. Herxheimer found, in a case of osteomalacia, one parathyroid gland larger than the others. On section of this gland large discrete masses of cells were seen containing large hyperchromatic nuclei with complete lack of fat, but the old tissue contained fat. However, he also found a similar gland in a normal person. Schmorl frequently found hyperplasia of the parathyroid gland in cases of osteomalacia and in one case of rickets in a human being; in three other cases of rickets the glands were normal. Similar observations were made by Todyo, who found hyperplasia in four of twenty-four normal persons, in six of seven senile persons with osteomalacia, in eight of eleven senile persons with osteoporosis, and in one person with osteitis deformans.

Parreira and Castro Friere reported a parathyroid tumor about 1.5 cm. in diameter occurring in the right side of the thyroid gland in a case

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of osteitis fibrosa. He noticed many mitotic figures in the tumor. Erdheim (6) found large tumors of the parathyroid gland in two cases of late rickets.

The experimental feeding of parathyroid glands of sheep to rachitic children produced a marked increase in the calcium and phosphate deposits in the bones, and a markedly increased ability to retain these salts (13).

Bergstrand believes that there is a plausible relationship between the enlargement of parathyroid glands and skeletal diseases, although it is not constant in osteomalacia. In other cases parathyroid tumors or enlargements of the gland accompanied nephritis, tetany, eclampsia, and epilepsy. He examined parathyroid glands in fifty cases of nephritis and found one or more enlarged glands in ten cases. In one case in this group there was considerable calcium deposit in the kidney.

Gold and Mandl each described a case of osteitis fibrosa in which a large, hard nodular tumor with a connective tissue capsule was found near the lower pole of the thyroid gland. These tumors were approximately 2.5 cm. in diameter. Histologically they were composed chiefly of large clear cells arranged in a lobular and cord-like fashion. Mandl noted in his case polymorphism of the cells with many mitotic figures, thus suggesting the possibility of malignant adenoma.

MacCallum described a case of chronic nephritis in which he found a tumor 2 cm. in diameter in the region of the thyroid gland. On section, the tumor was homogenous and slightly granular, and in the center there was a small cavity with smooth walls, containing clear fluid. Histologically the tumor consisted of loose and compact masses of clear cells with staining variations arranged as anastomosing branches or in columns lying in a delicate connective tissue stroma. De Santi, Benjamins, Erdheim (5), Hulst, Guy, and von Verebély reported similar tumors which correspond to the position of the inferior parathyroid glands. The tumors varied in size from about 1 to 12 cm. in diameter. Their consistence varied from a fluctuating to a solid mass and some contained cysts of varying sizes. They produced only local symptoms.

Malignant tumors of the parathyroid glands are extremely rare. The diagnosis is difficult, and extreme caution must be taken to distinguish them from certain tumors of the thyroid gland. Kocher (19) reviewed eight cases of tumors arising from the parathyroid glands, three of which were described by Langhans. Herxheimer, however, did not record a case of malignant tumor of the parathyroid glands except one described by Roffo and Landivar, and he was not able to obtain the original article for confirmation.

Of the eight cases reviewed by T. Kocher (19), two were described by A. Kocher and three by Langhans. The patients were aged between forty-six and sixty-eight years, and the tumor was more commonly found in males. Usually the tumor had been present for many years, having the character of a slow-growing goiter. The largest tumor was approximately

12 cm. in diameter. The tumor was usually nodular and fixed and the consistence in some was hard and in some elastic. In most of the cases there were disturbances of deglutition, respiration, and phonation. Only occasionally was there pain, which radiated to the back of the neck, shoulder, and ear. Enlarged cervical lymph nodes were present in a few cases; dilatation of superficial veins occurred in two cases, and venous thrombosis in one case. Histologically these tumors were composed of tissue resembling that of a parathyroid gland, the predominating element being the large clear cell. All of them contained glycogen and colloid-like or mucinous material. Some also contained the canals of Kurnsteiner, and most of them were associated with tissue of a sarcomatous character, and in some instances showing giant cells. Because of the metastasis, Kocher considered all of these tumors malignant. In one of his cases the tumor invaded the near-by muscles and veins, in another the trachea and esophagus, and in a third the trachea. In one of A. Kocher's cases there was metastasis into the pleura, lungs, and bronchial lymph nodes, and in the other, into a near-by vein. In Langhans' cases the tumors metastasized into near-by muscles and cervical lymph glands; in one case metastasis was noted into the scapula four years after operation.

De Quevain reported a case in which there was invasion of the jugular vein and sternocleidomastoid muscle, and five months later pulmonary metastasis as well as local recurrence developed.

Roffo and Landivar described the case of an Italian laborer, aged sixty years, who at the age of twenty-five, while in Italy, noticed a tumor about 1 cm. in diameter at the lower left pole of the thyroid gland. The tumor grew very slowly until one year before the patient entered the hospital, when he had noticed a second enlargement on the side of the neck. Six months later a small suprasternal tumor appeared which caused an aching pain, but was relieved when the patient was in the reclining position.

The tumor in the region of the thyroid gland became about 8 cm. in diameter and was divided into two parts: anterior and posterior, the latter corresponding to the cervical enlargement. Roentgenograms disclosed a mediastinal tumor as large as 10 cm. in diameter which was adherent to the surrounding structures and pulsated with the pulsation of the aorta; its volume, however, was not increased with pulsation.

At operation, the tumor attached to the thyroid gland and the lateral or posterior portion in the neck were removed and the mediastinal tumor was explored. The extirpated tumor, which was 10 cm. in diameter, was lobulated and clothed in a fibrous capsule which sent many trabeculae into the tumor, some of which contained calcium deposits. On section, the tumor was grayish-white and contained a few cavities, varying in size and filled with colloid-like material. The lateral or posterior mass consisted of eight nodules varying in size from 1 to 4 cm. in diameter which on section were also grayish-white with hemorrhagic and colloid-like areas.

Histologically the neoplastic tissue was composed of follicles with

columns of cylindrical cells containing nuclei in mitosis. In many of these follicles proliferated epithelium with large vesicular nuclei were present; the follicles were surrounded by connective tissue.

This patient died four months after operation, and at necropsy it was found that the primary tumor had recurred in the region of the thyroid gland and metastasized to the lungs and liver. The neoplasm and the metastatic growths were composed of elongated and polyhedral cells with well defined limits; these two types were believed to be anaplastic. The thyroid gland was invaded by the neoplastic tissue at the time of recurrence. The origin of this tumor was probably in an internal parathyroid gland.

Fasiani described a malignant adenoma of the parathyroid gland occurring in a woman aged sixty-five years, who had a goiter on the right side. A small nodule appeared on the left side which grew rapidly, causing pain in the left ear and shoulder. There was a mass about 10 cm. in diameter on the left side of the neck which was elastic, movable, nodular and painful. The tumor contained many cavities and solid nodules and the neoplastic elements corresponded to those of the parathyroid gland. Mitosis and invasion of the thyroid tissue were marked.

Ferrero and Sacerdote reported a case of a tumor with the structure of the parathyroid gland, which had developed in the femur. During the examination of the patient by the physician the femur fractured, but it healed in the usual period. The patient had noticed, for fourteen years, a small tumor on the right side of the neck. A month after the fracture a metastatic growth appeared in the right temporal bone. The metastasis seemed to be of a benign nature.

Alessandri reported a case of combined thyroid and parathyroid tumor metastasizing together or to the same place. The patient, a man, fell on the right shoulder and within a year sustained another injury of the same region. Two years later he again fell on the same shoulder and enlargement of the bone followed. At operation a large, hard, elastic, cystic tumor was found on the upper end of the right humerus. The thyroid gland was normal. After remaining well for twenty-one months a small tumor appeared near the humeral stump, which slowly increased in size and invaded the whole posterior region of the arm and axilla. Ten years after the first injury, intrascapular thoracic disarticulation occurred. The tumor was composed of two different types of tissues: one type, vesicular, tubular or alveolar, and lined with cuboidal or cylindrical cells most of which contained colloid secretion, and the other tubular or alveolar without any colloid secretion; its cells were larger and polyhedral, with a light staining protoplasm. These cells lay in a stroma of thin connective tissue with numerous broad and varicosed capillaries. The first tissue imitates thyroid tissue in different fields, like embryonal thyroid, adult thyroid, and adenomatous thyroid tissues. The second imitates the parathyroid gland.



The tumor in the case of hyperparathyroidism observed at The Mayo Clinic (reported by Wilder in this issue of this *Journal*) was situated in the carotid triangle, substernally in the right lobe at the inferior pole of the thyroid gland. Two-thirds of the right lobe and isthmus, with the tumor, was resected. The left lobe was explored and found to be normal. The tumor measured 5 by 3.5 by 3 cm. and weighed, including the portion of the thyroid tissue attached, approximately 40 gm. It was nodular, bluish-gray, fluctuating in parts, elastic and firm elsewhere, and was surrounded by a thick fibrous capsule (Fig. 1).

The cut surface of the tumor consisted of four distinct lobulated masses. The largest measured 2.5 cm. in diameter. The cysts were irregular and filled with amber-colored serous fluid. A large portion of the center of the nodules was bluish-red, and spongy in consistence. The periphery of the nodules was firmer and yellowish-brown, containing a few

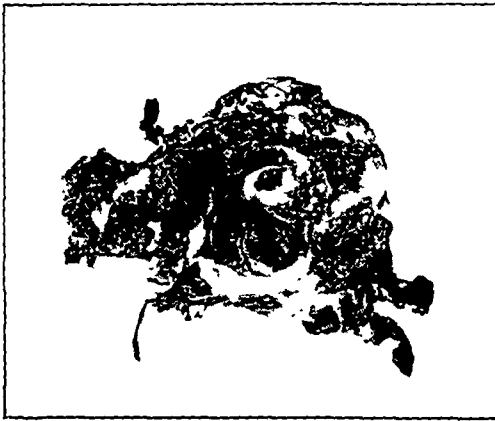


Fig. 1. Gross appearance of tumor.

petechial bluish-red spongy areas. The next largest nodule, which was 1 cm. in diameter, did not contain cysts, but had bluish-red areas of varying size. The two smaller nodules were firm, yellowish-brown and were not so sharply limited by a fibrous connective tissue capsule (Fig. 2). The thyroid tissue resected with the tumor was of the normal adult colloid type.

Microscopic examination of sections of all the nodules of the tumor disclosed the usual architecture of the parathyroid gland. It was lobulated, compact, tubular or cord-like, or rectangular with intervening spaces lined by endothelium on which rested the base of the epithelial cells. The capsule divided and subdivided the nodules. Within the walls of the septum there was parathyroid tissue; the fibrous walls had no connection with the stroma of the tumor. The cells were spheroidal, cuboidal, and polygonal, with poorly staining cytoplasm. The nuclei were variable in size, vesicular or homogeneous, and rich in chromatin material. Throughout the protoplasmic masses were many vesicle-like spaces around which the cells were arranged, giving a palisade effect (Figs. 3, 4, 5 and 6).

In every nodule there was a tendency of the cellular elements to group themselves into cords or branching tubules separated by vascular spaces

lined by endothelium. The stroma of the nodules was almost completely formed by these capillary vessels, in some parts reënforced by connective tissue fibrils. The capillary network was completely independent, as could be seen where the tumor invaded the connective tissue barriers and capsule. The cellular elements which constituted the tissue of the neoplastic portion of the nodules was composed of large, clear cells with poorly staining cytoplasm, polygonal in shape, and containing variable sized nuclei with deeply staining, coarsely granular chromatin material. There were also band-like masses of more deeply staining cells in which the cellular limits could not be seen very clearly, containing vesicular nuclei with abundant chromatin material. The nuclei of these cells varied greatly in size, as did the size and number of chromatin granules. The largest nuclei were ap-

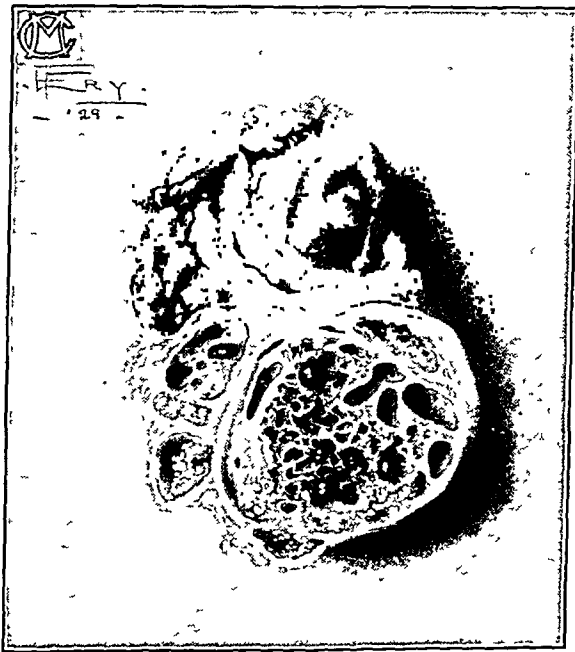


Fig. 2 Cross-section of tumor with thyroid gland attached

proximately seven times the size of a normal nucleus. Many mitotic figures were present. Along the capsules and fibrous tissue barriers especially, three types of cells were seen: (1) amorphous protoplasmic masses with lymphoid-like nuclei of varying sizes; (2) larger cells with more deeply staining, finely granular cytoplasm containing ovoidal or spheroidal nuclei of varying sizes, with deeply staining homogeneous chromatin material, and (3) large, clear polygonal cells with poorly staining cytoplasm but well defined cell limits, containing vesicular nuclei rich in chromatin material. These groups of cells follow the normal architecture of the normal parathyroid gland. Nowhere were the so-called foam cells found. This normal parathyroid tissue as well as the neoplastic elements was found within the fibrous tissue capsule, fibrous tissue septums, or barriers.

Throughout the neoplastic tissue there were many vesicle-like spaces somewhat similar to those seen in the thyroid gland. Their shape was

round, elongated, tubular or branched. These spaces contained, in some instances, thin, faintly pink-staining albuminous colloid-like material; others contained a bubble-like albuminous substance, and most of them contained blood in its various states. The faintly pink-staining albuminous colloid-like material was also seen in the capillaries, which in some places dilated into small "lakes." Some of these vesicle-like spaces were lined by cells giving the appearance of cuboidal or columnar epithelium.

The walls of the large cysts consisted of fibrous connective tissue; within and attached to their walls was normal and neoplastic parathyroid tissue. Scattered through the fibrous tissue was a variable quantity of hemosiderin and a very small amount of fat.

The histologic character of this neoplasm permits differentiation of it from most known thyroid tumors. In the fetal parathyroid glands the cells were compact with indefinite outline, whereas the adult gland was chiefly composed of large, clear cells with definite outline. In the adult gland

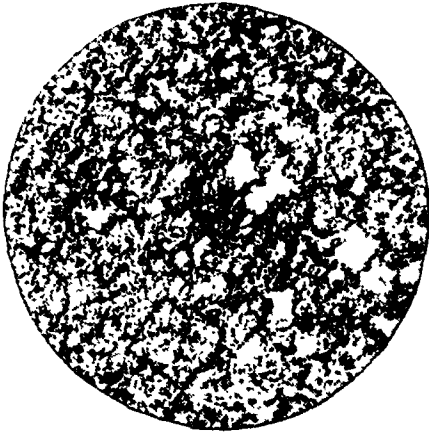


Fig. 3. Vesicle-like spaces in neoplastic tissue (x50).

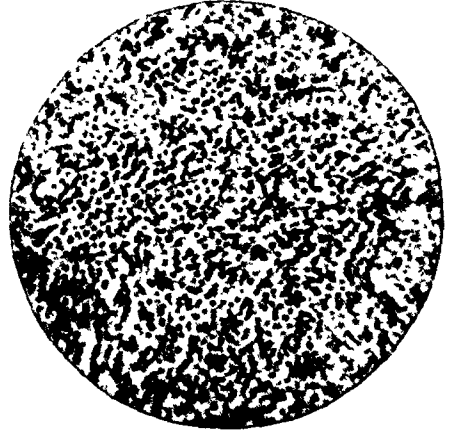


Fig. 4. Neoplastic tissue in same tumor as that shown in Figure 3 (x100).

there were also lymphoid-like cells and foam cells with varying amounts of fat among the cells and in the thin connective tissue stroma. Often there were vesicle-like spaces containing pink-staining albuminous material. It was not possible to determine the presence of glycogen, but in the neoplasm there were no true vesicles containing colloid, nor was there any fat or fatty tissue present.

In all of the tumors described in the literature, whether hyperplastic or true tumors, there seemed to be a concurrence in the finding of large, clear cells as the predominating neoplastic element. In some of the tumors described by Kocher there were also various cells and cell arrangement simulating sarcoma, and in a few instances there were giant cells. In some of the metastatic growths this sarcomatous tissue was present. Many of the tumors described contained cysts lined by squamous, cuboidal, columnar, and even ciliated epithelium. Sheard and Higgins noted, in the hyperplastic glands in chicks, cysts lined with squamous and cylindrical epithelium. This same picture has been noted in tumors of parathyroid glands

of the dog, cat, rabbit, sheep, and kinkajou (10). Epithelium was not found lining the cysts in this tumor.

The cases of Kocher, Langhans and Roffo were proved to be malignant by the occurrence of metastasis. Suggestion of malignancy was noted by Mandl and MacCallum, and Parreira and Castro Freire, in the tumors the diagnosis of which was based on the polymorphism of the cells and the presence of mitotic figures. Fasiani diagnosed the tumor in his case as malignant adenoma, particularly because of the invasion of the neoplastic elements into the neighboring thyroid tissue, the presence of a small amount of glycogen, and the frequent occurrence of mitosis. The diagnosis of malignancy in the case observed at The Mayo Clinic was based on the polymorphism of cells, the hyperchromatic nuclei with many mitotic figures, and the invasion of the neoplastic element into and through the capsule. The small nodules around the large nodule may be local and metastatic or each a primary tumor. The absence of fat and foam cells was striking (Figs. 5, 6 and 7).

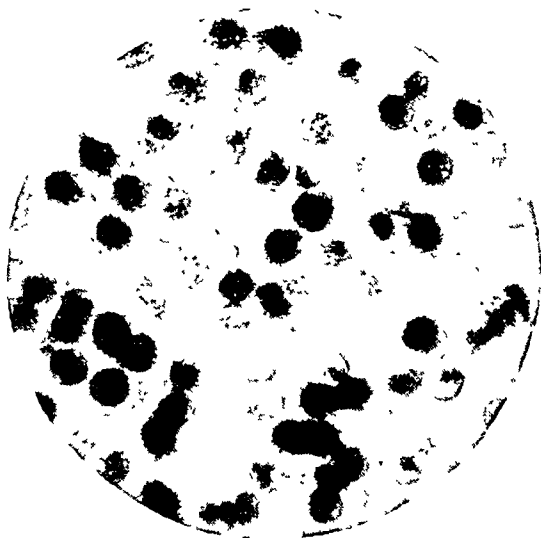


Fig. 5. Cells from normal accessory parathyroid gland ( $\times 750$ ).

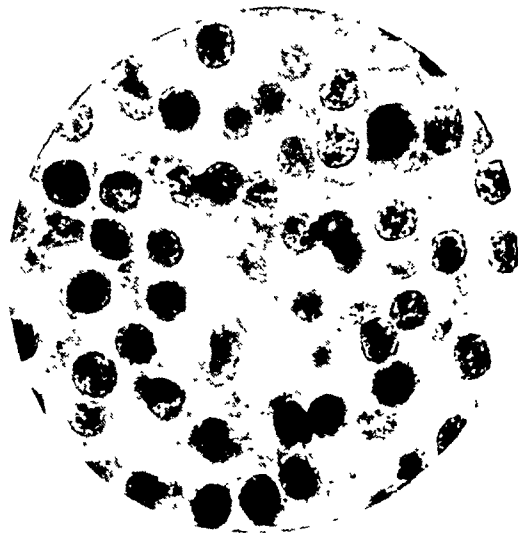


Fig. 6. Cells from neoplasm ( $\times 750$ ).

These tumors may possibly arise from included parathyroid glands, accessory parathyroid glands, aberrant parathyroid glands or tissue, or from a normally situated parathyroid gland. Parathyroid glands have been found in a cluster of three, thus making possible a triple tumor origin (32).

Pappenheimer and Minor considered the hyperplasia of the parathyroid glands found in rachitic children as due to the multiplication of the cells without increase of the supporting connective tissue. In the majority of cases of hyperplasia of the parathyroid gland there is an increase of the clear or chief cells, indicating that these are the functioning cells of the gland and that they are the predominating cells in the normal adult gland. This is noted in the many tumors of the parathyroid glands which have been found associated with skeletal diseases. Hoeffheinz reported a

case of osteitis fibrosis associated with hyperplasia of an internal parathyroid gland. He reviewed forty-four cases from the literature of glandular enlargement occurring in skeletal diseases and also in other conditions. He considered the hyperplasia as merely an increase in the number of cellular elements, and did not agree with Erdheim that there is in the cases of skeletal diseases a characteristic increase in the oxyphilic cells. Kerl be-



Fig. 7. Invasion into capsule of neoplasm is shown (x40).

lieves that the histologic changes found in these glands are secondary to the skeletal disease, since lesions in other endocrine glands have not been demonstrated. In Guy's case three nodular swellings appeared in the neck in the position of the parathyroid gland ten months after the removal of the parathyroid tumor. These nodules were thought to be due to compensatory hyperplasia rather than metastasis.

#### SUMMARY

The tumor observed in The Mayo Clinic, which measured 5 by 3.5 by 3 cm., was nodular, bluish-gray, fluctuating and semi-elastic in consistence, and clothed in a fibrous capsule. It was situated at the lower pole of the right lobe of the thyroid gland. On section, it consisted of four distinct encapsulated nodules composed of yellowish-brown, fairly firm, and reddish-blue spongy tissue, containing several cavities varying in size and filled with amber-colored fluid. The general structure was that of the parathyroid gland, made up chiefly of large clear cells. The tumor was diagnosed malignant adenoma because of the polymorphism of the cells and the hyperchromatic nuclei, the presence of mitotic figures, the invasion of the neoplastic tissue into the capsule, and the striking absence of foam cells and fat.

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# Abstract Department

**A comparison of the effects of adrenalin and pituitrin on the portal circulation.** Clark, G. A., *J. Physiol.* **66**: 274. 1928.

Portal pressure is increased by adrenalin and decreased by pituitrin, the latter action depending on vasopressin. Both reduce blood flow through the liver.—C. I. R.

**Influence of epinephrine on blood sugar utilization of functional hepatectomized rats.** Cori, C. F. and G. T. Cori, *Proc. Soc. Exp. Biol. & Med.* **26**: 345. 1929.

After a preliminary subtotal ligation of the portal vein the whole liver pedicle was tied off in rats under amytal anesthesia and glucose was infused intravenously at a constant rate (110 mgm. per 100 gm. per hour). In all cases the sugar and lactic acid content of the blood was higher when epinephrine was injected subcutaneously (0.02 mgm. per 100 gm.) at the beginning of the infusion. The blood sugar was 246 mgm. per cent, the blood lactic acid 135 mgm. per cent when epinephrine was injected (average 10 experiments). With glucose alone the blood sugar was 134 mgm. per cent, the blood lactic acid 55 mgm. per cent (average 10 experiments). When the hepatic pedicle was tied, but no glucose injected, the rats developed the typical symptoms associated with hypoglycemia, which could be relieved by the injection of glucose. —G. T. Cori.

**Immunologic studies in relation to the suprarenal gland.** Marmorston-Gottesman, J. and D. Perla, *J. Exper. Med.* **48**: 225. 1928.

The effect of subcutaneous injections of varying amounts of epinephrine on the hemolysin formation of normal adult albino rats was studied. In one group of experiments the rats received 0.4 mgm. per kgm. per day in two injections during 3 days prior and 4 days subsequent to the injection of sheep cells. Another series received the same daily amounts, but only during 4 days subsequent to the injection of antigen. A third series received the same daily amounts only during 1 day prior and 2 days subsequent to the injection of sheep cells. In a second group of experiments smaller amounts of epinephrine were given during 3 days prior and 4 days subsequent to the injection of antigen. The amounts used were  $1/5$ th,  $1/20$ th,  $1/40$ th, and  $1/60$ th the daily quantity of epinephrine injected in the first group of experiments. Large amounts of epinephrine injected repeatedly before and after the injection of antigen depress the antibody forming capacity of normal adult albino rats to a marked degree. The depression in antibody formation is roughly proportional to the quantity of epinephrine injected. Small amounts have no detectable effect on antibody formation.—J. Marmorston-Gottesman.

**On the supposed existence of pro-adrenin in the adrenals (*Sur la prétendue existence d'une adrénaline virtuelle dans les surrénales*).** Molinelli, E. A. and P. Mazzocco, *Compt. rend. Soc. de biol.* **99**: 1001. 1928.

The bichloride color test (Bailly's) indicates that there is less adrenin in the adrenals at the time of death than 24 hours later. Post mortem changes in an assumed pro-adrenin are called on to account for this. When the pressor effect in a dog is used as an indicator, it is proved that there is no actual increase in adrenin post mortem. Both Bailly's test and that of Folin, Cannon, and Denis are inaccurate where 24-hour material is used.—J. C. D.

**Adrenalin and fatigability of muscle of adrenalectomized rats.** Nice, L. B., D. S. Greenberg and S. L. Greenberg, *Proc. Soc. Exper. Biol. & Med.* **26**: 136. 1928.

In 11 adrenalectomized rats given injections of adrenalin chloride (1 cc. of 1:50,000) over periods of 9 to 84 days, there was no evidence of increased work done by the gastrocnemius muscle.—M. O. L.

**Effect of ergotamin tartrate, adrenin, and atropine on the tension of the cerebrospinal fluid** (*Influence du tartrate d'ergotamine, de l'adrénaline et de l'atropine sur la tension du liquide céphalorachidien*). Urechia, C. I. and L. Dragomir, *Compt. rend. Soc. de biol.* **99**: 1069. 1928.

Adrenin raised the pressure in nine out of ten cases.—J. C. D.

**Presence of adrenin and choline in lymph** (*Présence d'adrénaline et de choline dans la lymphe*). Viale, G., *Compt. rend. Soc. de biol.* **99**: 1009. 1928.

Examination of fluid from the thoracic duct of dogs showed 18 mgm. per litre of choline. This dropped to 4 mgm. or less when the adrenals were removed. Lymph from normal dogs, when tested on frog's heart, on frog's eye, and for its pressor effect, gave the reaction for adrenin. This was not present after the adrenals were removed.—J. C. D.

**The influence of adrenalin and of some other internal secretions on contraction of mammalian skeletal muscle** (*Über den Einfluss des Adrenalins und einiger anderer Inkrete auf die Kontraktionen des Warmbluterskelettmuskels*). Wastl, H., *Arch. f. d. ges. Physiol.* **219**: 337. 1928.

A statistical study was made of the influence of intravenous injections of various doses of adrenalin on the contraction of the tibialis anterior muscle when stimulated electrically through its nerve between 120 to 160 times per minute in urethanized cats. In 236 experiments the form of the muscle curve was changed in four groups, showing (1) a reduced height of contraction in 21% of the male and 37.2% of the female animals; (2) an increase in the amplitude of contraction in 37.2% of the males and 19.3% of the females; (3) a short increase in the height of contraction occurring synchronously with the rise in blood pressure, which was followed by a decrease in 25.8% of the males and 19.3% of the females; (4) no effect with very small doses in 11.6% of the males and 24.2% of the females. The results indicate that the muscle curve is influenced by adrenalin only through its effect on circulation. Thyroid extract had no effect on muscle contraction, while "hypophysin" stopped the muscle contraction apparently by asphyxia.—L. B. Nice.

**Increase of blood platelets by spleen contraction caused by adrenalin** (*Mobilisation des plaquettes par l'adrénaline* *Plaquettose par spleno-contraction adréalinique*). Binet, L. and M. Kaplan, *Compt. rend. Soc. de biol.* **97**: 1659. 1927.

The intravenous injection of 0.1 mgm. adrenalin per kgm. of body weight into dogs anaesthetized with chloralose caused, within five to fifteen minutes, a great increase in the number of platelets in the blood from the carotid or femoral arteries. After splenectomy the blood of these same animals showed practically no change in the number of platelets following the introduction of adrenalin. A negative result was obtained from adrenalin following an injection of yohimbine.—L. B. Nice.

**The clinical manifestations of ovarian dysfunction.** Chalfant, S. A., *Penn. M. J.* **32**: 332. 1929.

The clinical evidences of ovarian dysfunction are the various menstrual disturbances and sterility. In most cases the administration of ovarian preparations is based on inaccurate diagnosis, and there is little knowledge of the potency of the preparation and its fate after administration. However, the use of ovarian extract in the control of spontaneous or surgical menopause seems to be of definite value.—I. B.

**The relation between concentration and action of adrenalin.** Wilkie, D., *J. Pharmacol. & Exper. Therap.* **34**: 1. 1928.

Responses of arterial strips, cardiac output, and blood pressure to adrenalin were studied. When physiological concentrations are present, the effect varies almost directly with the concentration, while with toxic concentrations, the effect varies as the logarithm of the concentration.—C. I. R.



On the influence of the removal of thyroid gland, gonads, and spleen upon the formation of agglutinins in active immunization by typhoid bacilli. Bochkareff, P. V. and E. P. Chernosatonska, *Vestnik Endocrinology*, 2-3. 1929.

The authors confirmed in this work their previously reported findings that the removal of the thyroid gland, gonads, and spleen leads to a reduction of hemolysins for a long time after the operation. They produced an active immunization in 50 rabbits by typhoid bacilli. Most of the rabbits were immunized once before and several times after the operation, at varying intervals. The immunization of the control rabbits was repeated at definite intervals. The agglutinins of the experimental rabbits were gradually decreased with each new immunization, and after several months they proved to be 5-10 times less than the original titer before operation. The titer of the control rabbits was unchanged, in some it increased, and in one it decreased to  $\frac{1}{2}$  of the normal titer. The lowest titer was in the splenectomized rabbits. Trauma, such as caused by laparotomy, did not lead to a reduction of the titer.—Olga Sitchevska.

On the influence of the removal of thyroid gland, testicle, and spleen upon the titer of the hemolytic amboceptor in active immunization. Bochkareff, P. V. and E. P. Chernosatonska, *Vestnik Endocrinology*, 2: 417. 1928.

The authors produced an active immunization in 36 rabbits by injections of a 40% emulsion of erythrocytes of sheep. Fourteen rabbits served as controls, 8 were splenectomized, 6 were castrated, and 8 thyroidectomized. The titer of hemolysins in the serum was then determined. Some of the rabbits were immunized a second time in 1-3 months. The conclusions are as follows: The removal of the thyroid, testicle, and spleen leads to a considerable reduction of hemolysins in blood. This result was obtained after a considerable length of time after the operation. The reduction of hemolysins is not specific for any of the glands, but seems to be due to the disturbance of hormone equilibrium caused by the removal of one or all organs of the endocrine system.—Olga Sitchevska.

The isolation of secretin; its chemical and physiological properties. Mellanby, J., *J. Physiol.* 66: 1. 1928.

A new method for preparation and purification of secretin is described. It is a polypeptide containing phosphorus. Its chemical characteristics are described. Secretin acts best intravenously and is not absorbed from the intestine. It does not affect blood sugar but increases the external secretions of the pancreas and liver. In physiological concentrations in the blood it does not affect smooth muscle but in stronger concentrations it will increase tonus. It produces local vasodilation in the pancreas but does not affect blood pressure in general. It has no effect on respiration, skeletal muscles, or secretory activity of the kidney.—C. I. R.

Modification of endocrine glands following insufficient alimentation in man (Les modifications des glandes a secretion interne a la suite d'une alimentation insuffisante chez l'homme). Stefko, W. H., *Rev. frang. d'endocrinol.* 6: 103. 1928.

The author finds that the thyroid colloid changes from acidophylic to basophylic and that hypoplasia and atrophy follow. The parathyroids increase in volume. There is a diminution of Hassall's corpuscles in the thymus. Suprarenal changes are evidenced by a thinning of the capsule and cortical hemorrhages. The growth of the genital gland is greatly retarded. The pineal is unchanged when the subject is under 6-7 years. It reverts to the 6-7 year condition in subjects about 14-16 years. Regeneration of the pineal gland is found to occur in adult females.—B. Cunningham.

Pluriglandular syndrome involving calcium deficiency and correlated with behavior disturbances. Timme, W., *Arch. Neurol. & Psychiat.* 21: 254. 1929.

A large proportion of 24 patients presented in varying degrees close resemblances to one another in several important particulars: gross behavioristic abnormalities (quick temper), with deficient utilization of calcium, parathyroid

deficiency and pineal involvement, and with secondary disturbances in growth, blood pressure and gonadal development. This syndrome is easily recognizable, is frequently encountered and lends itself to therapeutic attack. Considerable success was attained by the use of calcium lactate, sunlight and parathyroid extract. This was seen particularly in growth and in lessened irritability.

—R. G. H.

**Experimental investigations on the bodies of Kurloff** (*Recherches experimentales sur le corps de Kurloff*). Alexeieff, A. A. and N. Joukoff, *Compt. rend. Soc. de biol.* 98: 34; 446. 1928.

The bodies of Kurloff are the azurophile inclusions seen in the lymphocytes of guinea pigs. These are found in the peripheral blood and spleen after puberty. Splenectomy does not abolish them. They disappear following gonadectomy or double ligation of the ductus deferens. Replacement of the sex hormone either by injection or transplantation causes the bodies to reappear unless too much time (seven months) has elapsed since the operation. The number of bodies is increased during pregnancy, one rise occurring on the 7th and another on the 12-13th day. The bodies chemically represent a lipase and may be related to Evan's vitamine F.—J. C. D.

**Effects of ovariectomy upon menstruation in monkeys.** Allen, E., *Am. J. Physiol.* 85: 471. 1928.

The interruption of ovarian endocrine function by ovariectomy toward the end of the second week of the menstrual cycle (just following ovulation in 3 cases) caused the onset of menstruation in 3 to 5 days after operation. This is an acceleration of 7 to 11 days, estimated upon the expectation of cycle length in the normal monkeys. These postoperative menses were more profuse and of longer duration than normal menses. In ovaries of only three animals were recent corpora lutea found. In the other animals ovulation had not recently occurred. The ovaries of these animals contained several (often many) moderately large follicles. It is concluded that (a) if ovulation occurs, the corpus luteum in the monkey may continue to secrete ovarian hormone somewhat similar to that secreted by follicles or (b) if ovulation does not occur, large or atretic follicles may continue this endocrine function. The chief effects of this hormone in monkeys are the induction of growth in the genital organs to a functional condition and the maintenance of "sexual skin" phenomena. Menstruation appears to be degenerative in significance and at least partly due to decrease in amount, or in these experiments to absence, of ovarian hormone after a certain amount of growth and development of the endometrium had been induced by hormone action. The corpus luteum does not seem to be a necessary causative factor in the essential menstrual mechanism in the monkey.

—Author's Abst.

**Precocious sexual development from anterior hypophysis implants in a monkey.** Allen, E., *Anat. Rec.* 39: 315. 1928.

Four implants of anterior lobes of hypophyses of mature monkeys were made at two day intervals in an immature female monkey. This treatment caused premature development of secondary sex characteristics and growth in the genital organs and mammary glands. The ovaries were greatly enlarged due to a marked stimulation of growth of the follicles. More than thirty large follicles had developed in each ovary,—several were apparently on the verge of ovulation. The effects upon sex characteristics and growth of the genital tract and mammary glands are similar to those obtained in castrated monkeys from injections of hormone from ovaries and placenta. These effects in the present experiments were apparently secondary to ovarian development, for it was noted by Smith and Engle that anterior lobe implants have no effect on castrated animals. Similar experiments with implants of anterior lobes from dogs into immature monkeys gave negative results. The anterior lobe of the hypophysis of the monkey contains considerable gonad stimulating hormone.—Author's Abst.

**Effect of thyroid administration upon the testes of the albino rat** (*Über die Wirkung der Thyreokrinfütterung auf die Hoden der weissen Ratten*). Belawenetz, S., *Anat. Anz.* 65: 154. 1928.

Fifty-five male white rats were given thyroid in the form of a dried powder mixed with lard. The size of the dose for each age was determined by experiment and was as great as could be borne without the exhibition of toxic symptoms. The longest experiment extended over six months. The observer records degeneration of the testes which appeared whether the animal was sexually mature or not. The younger the animal at the beginning of treatment the more complete was the degeneration. In spite of the gradual increase in dosage regeneration takes place, its time of appearance depending upon the age of the animal. Regeneration is accomplished by the division of residual spermatogonia and not by the division of the Sertoli cells. During the experiment loss of sexual desire and potency were observed.—W. J. A.

**Histology of the ovary in amenorrhea** (*Histopathologia del ovario en la amenorrea*). Blanco, J. T., Arch. de med., cir. y espec. **29**: No. 16. 1928.

This paper attempts to analyze ovarian hypofunction as the cause of amenorrhea. The effects of tumors and inflammation as destructive of follicular elements are well known. Rarer conditions are those in which sclerotic changes prevent the rupture of graafian follicles and those in which disease affects the ovarian parenchyma adversely—not by direct destruction of the tissue elements but through chemical effects of the disease producing organisms.  
—C. Hartman.

**Cause of hen-feathering in Campine and Bantam males.** Danforth, C. H., Proc. Soc. Exper. Biol. and Med. **26**: 86. 1928.

Skin grafts taken from chickens of either sex and implanted on ordinary male hosts produced typical cock feathers when the donor was from a strain (such as the Leghorn) showing sexual dimorphism in plumage, but hen feathers when the donor was from a strain not showing this dimorphism (Campine or Sebright Bantam). Since the same body fluids circulate to the tissue of both graft and host, the observed results indicate that an essential difference between hen-feathered and cock-feathered males is a differential responsiveness of the feather follicles to the same endocrine stimulus.—Author's Abst.

**Calcium and phosphorus balances in rats during period of pregnancy and lactation.** Goss, H. and C. L. A. Schmidt, Proc. Soc. Exper. Biol. & Med. **26**: 104. 1928.

After the onset of pregnancy and prior to parturition, the animals stored calcium and phosphorus in excess over that estimated to be contained in the litter at birth. During the period of lactation, the assimilation of both calcium and phosphorus by the mothers increased markedly, but this increase was not sufficient in most cases to account for the storage of these elements by the young. The animals were consequently in negative balance.—M. O. L.

**The value of ovarian extract after an artificial menopause.** Haulain, W. F. T., Edinburgh M. J. **35**: 180. 1928. Transactions of Edinburgh Med. Soc.

Forty-four cases in which the ovaries had been removed are analyzed. Seven received no post operative ovarian medication. Twenty-four received ovarian extract by mouth and thirteen by mouth and by injection. The menopausal symptoms, particularly flushing, seemed to be relieved. The combined treatments gave better results than oral administration alone.—J. C. D.

**The duration of pregnancy in guinea-pigs after removal and also after transplantation of ovaries.** Herrick, E. H., Anat. Rec. **39**: 193. 1928.

Ovaries were removed from 32 pregnant guinea-pigs. Into 14 of these were implanted ovaries from other animals, mostly virgin. It is found that ovariectomy in pregnant animals usually causes abortion, but that it is possible for pregnancy to continue even if the ovaries are removed before the middle of the gestation period. The implantation of ovaries from virgin animals following ovariectomy usually prevents abortion in guinea pigs. It is concluded that the presence of an ovary tends to prevent abortion, but that the active substance is not confined to the corpus luteum of pregnancy. Removal of the

ovaries, even before the mammary glands begin to enlarge, usually does not prevent lactation, nor does it prevent the pelvic girdle from relaxing at the time of parturition. It is further found that when abortion results from the removal of the ovaries, it usually occurs several days after the operation.

—W. J. A.

**Basal metabolism (oxygen) of normal women in relation to injection of follicular hormone.** McClendon, J. F., G. Burr and C. Conklin, *Proc. Soc. Exper. Biol. & Med.* **26**: 265. 1928.

The basal metabolic rate of one woman rose after subcutaneous injection of 300 mouse units of follicular hormone and fell after 880 units. The metabolism of a second woman fell after 1000 units; that of a third rose somewhat 7 hours after the injection of 1000 units; that of a fourth rose after 2000 units; that of a fifth remained constant after receiving 4000 units.—M. O. L.

**The distribution of the estrus producing and estrus inhibiting hormones in the ovary of the cow.** Payne, W. B., H. Van Peenan and G. F. Cartland, *Am. J. Physiol.* **86**: 243. 1928.

The cholesterol-free unsaponifiable fractions of the fat of corpus luteum and ovarian residue were assayed for their estrus producing and estrus inhibiting hormones. In terms of dried gland the corpus luteum contained 35 rat units and ovarian residue 66 rat units of estrus producing hormone per kgm. The minimal active dose of unsaponifiable material was 180 mgm. for corpus luteum and 40 mgm. for ovarian residue. The corpus luteum contained 42 guinea pig units of inhibitory hormone in the unsaponifiable fat from 1 kgm. dried gland. The inhibiting hormone was lacking in a similar extract of ovarian residue.—W. B. Payne.

**Sex-proportion in children and the thyroid gland of parents (*Die Verschiebung der Sexual-Proportion bei den Kindern und die Schilddrüsen der Eltern*).** Pfister, C. R., *Schweiz. Med. Wchnschr.* **58**: 1287. 1928.

This is a statistical analysis of the influence of goiter of parents on the proportion of male and female children; 2034 males and 2120 females are separated into 22 groups according to the goiter index of the father and mother. Four degrees of goiter (designated goiter index I, II, III, and IV) are recognized. The general conclusion is that the higher the goiter index of the parents the larger is the percentage of female children. The shift is from about 48 per cent females where parents have a low goiter index to about 52 per cent females in cases of parents with the highest goiter index.—A. T. R.

**The therapeutics of an active orchitic extract.** Plummer, C., *Practitioner*, **119**: 388. 1927.

Six cases, suffering from various phases of general debility with depression and nervousness, improved after injections of a testis extract—A. T. C.

**Experimental investigation of the internal secretion of the prostate (*Experimentelle Untersuchung über die Innersekretorische Funktion der Prostata*).** Yamashita, Y., *Folia Endocrinologica Japonica*, **4**: 8. 1928.

Although many attempts have been made to determine the existence of an endocrine function of the prostate, the results to date have been unsatisfactory. The author has worked experimentally on the problem both with healthy adult dogs whose prostate had been removed, as well as with dogs and rabbits injected with an extract of prostate from dogs and cattle. On these animals the author investigated the blood changes and the histological condition of the various other endocrine organs. The prostatectomized dogs showed a fall in the residual  $O_2$  (of the blood), and blood sugar. The  $O_2$  dissociation curve was lowered and the eosinophiles and lymphocytes in the blood showed a striking increase; the blood of dogs and rabbits injected intravenously or subcutaneously with extract of cow and dog prostate showed an increase in residual  $O_2$ , albumen and sugar and a decrease of lymphocytes, with a fall in the  $O_2$  dissociation curve. The prostatectomized dog developed a greater insulin hypoglycemia

than did a normal dog. On the other hand, the dogs given extract of prostate showed a slight hypoglycemia after insulin, the effect being the same as increasing the action of adrenalin on the blood sugar. The testes, thyroid, medulla of suprarenal capsule of the prostatectomized dogs gave the appearance of atrophy or degeneration. The islands of Langerhans were increased in size and number and the hypophysis increased in weight. In dogs injected with prostate extract from cows or dogs a picture was presented of hyperfunction of the prostate and thyroid, hypertrophy of the adrenal cortex, degeneration of the pancreas, smaller and fewer eosinophiles and an increase of the principle cells of the anterior lobe of the pituitary gland. Rabbits fed with "prostatin" showed a decrease in body weight, atrophy of the pancreas and thymus, a shrinking and lessening of eosinophile cells as well as an increase in the number of principal cells of the anterior lobe of the pituitary. The author believes that the prostate is related functionally to the endocrine glands, being especially antagonistic to the pancreas and acting synergistically with the thyroid.—Author's Abst. Translated.

**A contribution to the action of the ovarian hormone (Ein Beitrag Zur Wirkung des Ovarialhormons).** Van De Walle, F., Zentralbl. f. Gynäk. 51: 2622. 1927.

A report is made of results of subcutaneous injection of ovarian hormone two to three times a week in six cases of artificial menopause following hysterectomy, five cases of spontaneous menopause, one case of oligomenorrhea and two cases of amenorrhea in young women. It is stated that the ovarian hormone employed in this manner, even after a few injections, has a distinctly noticeable influence on the flushings, the appetite, digestion and nervousness. These symptoms of ovarian dysfunction were, however, not influence in a similar manner or to a like degree in the various patients. Three meager case reports are given of treatment for amenorrhea. One woman, age 22, had not menstruated for nine months. Yohimbin treatment was followed by one menstruation, but amenorrhea then persisted eight months until menstruation recurred following four treatments of ovarian hormone. In the second case, a neurasthenic woman, 30 years old, had amenorrhea for one year. No results were obtained from Yohimbin treatment. There was no treatment for one month, then ovarian hormone was injected three times daily. On the second day there was lower abdominal pain. On the fourth day menstruation began. One woman, age 48, had amenorrhea eleven months; three days after the first injection menstruation began and her subjective symptoms subsided. The case reports do not extend beyond one menstruation following injection.—J. P. Pratt.

**Ovarian cycle and insulin action (Ovarialzyklus und Insulinwirkung).** Vogt, E., Zentralbl. f. Gynäk. 51: 3034. 1927.

Insulin therapy in non-diabetics is now becoming an important phase in the study of this hormone. Various authors have shown that hyperthyroid symptoms are improved by insulin, psoriasis is improved, though not cured, and uterine bleeding of ovarian origin is often relieved. The types of bleeding from the uterus which are suitable for insulin treatment are grouped as metrorrhagia hemorrhagica, i. e., bleeding due to a dysfunction or insufficiency of the ovaries, coming most frequently at the beginning and the end of the reproductive period. A second indication is found in the menorrhagia due to acute or chronic inflammation of the uterus or adnexae. The author considers unsuitable for treatment with insulin, bleeding due to endometritis, submucous myoma, polyp and malignancy. The smallest possible doses which will give results are chosen. Two subcutaneous injections are given before the noon and evening meal. Hypoglycemia must be avoided. Three days' treatment is usually all that is necessary to obtain results. Two cases are cited in which amenorrhea was associated with loss of weight. As the weight increased with feeding and insulin therapy, the general condition improved and menstruation was re-established. The author considered this a direct action of insulin on the ovaries. Other authors are quoted as having had success in treatment of toxemia of pregnancy with insulin. Considerable theoretical discussion is given as to the mode of action of insulin on the ovaries, whether direct or indirect. There is a marked action of insulin on the female sex glands. The action of the insulin on the ovarian cycle in non-diabetics is theoretically and practically most important. In insulin treatment of non-diabetic women in the reproduc-

tive age, the dose should be modified according to the condition. Ordinarily, insulin treatment should begin just after menstruation and the dosage increased slowly during the first half of the intermenstruum. Treatment should not begin in second half of intermenstruum, and especially should the dose not be increased at that time on account of the greater sensitiveness to insulin. During menstruation, insulin injection should be discontinued.—J. P. Pratt.

**Effect of liver and pituitary digests on the proliferation of sarcomatous fibroblasts of the rat.** Baker, Lillian E. and A. Carrel, *J. Exper. Med.* **47**: 371. 1928.

Since it has been shown that the peptic digestion products of pure proteins are utilized by fibroblasts for growth in vitro, but that their nutritive action is supplemented by some substance or substances in fresh tissues, the experiments were extended to a study of the action of peptic digests of various glands and tissues on the growth of fibroblasts in vitro. It was found that digests of the anterior lobe of the calf or steer pituitary, and also of calf liver, caused not only a larger proliferation of fibroblasts than had previously been obtained in artificial media, but the rate of multiplication of sarcomatous fibroblasts of the rat was as great in these media as in embryo juice. These digests prove to be a complete food for sarcomatous fibroblasts of the rat, but do not prolong the life of normal tissues indefinitely. The nature of the substances present in these media which supplement the nutritive action of the protein split products has not been ascertained. They are not, however, of lipoid nature, as the growth-promoting power of the digests is not diminished by thorough extraction with ether.—Lillian E. Baker.

**The treatment of diabetes insipidus with pituitary posterior lobe extract applied intranasally.** Campbell, J. R. and H. L. Blumgart, *Am. J. Med. Sci.* **176**: 769. 1928.

Due to the inconvenience of repeated hypodermic injections, the intranasal method of administration of pituitrin was investigated. Two methods were used: in the first the obstetrical pituitrin was sprayed onto the roof of the nasopharynx with an atomizer; in the second method, a cotton swab was soaked with 0.5-1 cc. of pituitrin and placed against the roof of the nasopharynx. Most of the disturbing factors were eliminated as far as possible, so that an accurate comparison of these methods might be made with the hypodermic method. The intranasal applications were as efficacious as hypodermic injections in controlling the fluid intake and urinary output. Since pituitrin is absorbed by the lymphatics of the olfactory nerve cells, it is important that the cotton pledget be placed high in the nasopharynx.—E. L.

**Nerve fibers in the pituitary of the rabbit.** Croell, M. M., *J. Physiol.* **61**: 316. 1928.

By a complicated technic described in detail, non-medullated nerve fibers which are not vasomotor were demonstrated in the pars intermedia.—C. I. R.

**The hyperglycemic effect of vasopressin, oxytocin and pituitrin.** Geiling, E. M. K. and C. A. Eddy, *Proc. Soc. Exper. Biol. & Med.* **26**: 146. 1928.

The effect on blood sugar of the oxytocic and pressor principles of the posterior pituitary was studied in unanesthetized dogs and rabbits. Both substances caused a definite hyperglycemia. The rise of blood sugar with the oxytocic substance was more prolonged, but not as high as with the pressor substance.—M. O. L.

**Blood pressure in unanesthetized animals affected by "vasopressin," "oxytocin," pituitary extract and other drugs.** Gruber, C. M., *Proc. Soc. Exper. Biol. & Med.* **26**: 243. 1928.

In dogs and cats under chloretone anesthesia, vasopressin caused a rise in blood pressure. In unanesthetized animals the initial injection of vasopressin caused first a slight rise, then a marked fall in blood pressure, amounting in

some cases to 150 mm. Hg., and accompanied by a slow pulse, grouped cardiac contractions and decreased respiration. This was followed by a prolonged rise in pressure. Subsequent injections caused no fall in pressure.—M. O. L.

**Hypophyseal hormones in the guinea pig** (*Les hormones hypophysaires chez le cobaye*).

**Hypophyseal hormones and the "law of puberty"** (*Hormones hypophysaires et loi de la puberté*). Lipschutz, A. and R. Paez; A. Lipschutz and H. Kallas, *Compt. rend. Soc. de biol.* 99: 453; 454. 1928.

The pituitary body of adult guinea pigs of either sex yields, even after castration, an extract which, when injected into rats, produces the characteristic early development of oestrous. The glands of young animals, however, do not yield this substance in a quantity sufficient to more than cause a premature opening of the vagina. The hypophyseal hormone is probably the substance assumed to exist when the author formulated his "law of puberty," according to which the ovary was dependent for its development and activity on some hormone which was identical in both sexes.—J. C. D.

**The action of insulin and hypophysin on the output of urine, and especially on the carbon compounds in diabetes insipidus** (*Action de l'insuline et de l'hypophysine sur l'élimination urinaire et spécialement sur la carbonurie dans le diabète insipide*). Marinesco, G., O. Kauffman-Cosla and St. Drăganescu, *Compt. rend. Soc. de biol.* 99: 911. 1928.

One patient showed a polyuria and unoxidized carbon compounds in the urine. Insulin reduced the quantity of these compounds, but did not reduce the amount of urine. Hypophysin reduced the urinary output, but did not influence the amount of unoxidized carbon compounds. Another patient showed polyuria, but no excess of unoxidized carbon compounds. Here insulin had no effect, while hypophysin reduced the polyuria. The authors conclude that in diabetes insipidus insulin accelerates the cellular oxidation, while hypophysin acts on the urinary output.—J. C. D.

**Concerning hypophyseal and chondrodystrophic dwarfs** (*Im besonderen über hypophysaire und chondrodystrophische Zwerge*). Maas, O., *Med. Welt. Nr.* 39. 1927. *Abst., Monatschr. f. Kinderh.* 39: 493. 1928.

There are various types of dwarfs differentiated according to etiology and symptomatology. In certain types, the etiology, as yet, is unknown. Hypophyseal dwarfs show a marked disturbance of the internal secretion of the pituitary. They show no great abnormality in the proportions of their body structures, nor does the ratio of the length of the trunk to the length of the extremities show any striking anomaly. The feet, hands and head are surprisingly large compared with the length of the body. X-ray studies show frequently a delayed and incomplete ossification of the epiphyseal lines. Abnormal relations exist in the sella turcica. The sexual organs and the secondary sexual characteristics are imperfectly developed in these hypophyseal dwarfs. The condition is often familial in incidence, being found in several members of one family. In young hypophyseal dwarfs the mixture of infantile and adult facies makes a striking facial expression. Some hypophyseal dwarfs have attained a definite growth in relatively late years without any therapy. The sexual glands may play a rôle in the etiology of dwarfism. At times dwarfism can be seen in congenital lues and in children who die shortly after birth from congenital heart failure. Chondrodystrophy is the condition that has been most extensively investigated. In the chondrodystrophic dwarf the most striking anomaly is the relative length of the trunk. The extremities are very short. Other striking features are the size of the head, the prominence of the frontal and parietal bones, as well as the abnormally deep insertion of the nose. The forearms cannot be extended completely and the fingers are abnormally short. The Trident hand is characteristic and is due to the fact that the fingers cannot be opposed. Frequently one sees an abnormal development of fat in the region of the gluteals and thigh, as well as the so-called saddling of the lumbar portion of the spine. The relations of the length of the upper to the lower arm and the thigh to the leg are the

reverse of those obtaining in a normal individual. The author asserts that he has observed transitions from a normal development to chondrodystrophy. The etiology of the disease is not clear.—P. Solomon.

**The failure of pituitary substances to influence the basal metabolism or the specific dynamic response to food in a normal subject.** Missal, M. E. and Margaret W. Johnston, *J. Lab. & Clin. Med.* 14: 314. 1929.

Administration by mouth of whole pituitary substances (Wilson) and by intramuscular injection of antuitrin (Parke-Davis) and of pituitary solution obstetrical (Wilson) over comparatively long periods of time failed to influence the basal metabolism or the respiratory quotient in an apparently normal subject. The increases in the metabolism after administration of sucrose and glycine separately, were so irregular both with regard to time and magnitude of the maximal response, both during the control periods and also following the administration of the above substances, that conclusions regarding the effect of the administrations of pituitary substances upon the specific dynamic effect of food are unwarranted.—Author's summary.

**Sympathetic affections and diabetes.** Absence of the pilomotor reflex in localized areas (*Les troubles sympathiques et le diabète. L'aréflexie pilomotrice en aires*). André-Thomas, *Paris med.* 40: 280. 1928.

Some statements are made regarding pilomotor or "goose-flesh" reflexes, and five cases are quoted in which there occurs coincidentally with diabetes a disturbance of these reactions. In certain circumscribed but irregularly disposed areas pilomotor reflexes are found to be lacking. The reflexless areas may have a distribution similar to that of an eruption. Territories of the twelfth dorsal and first lumbar roots are specially affected, and areas supplied by anterior branches of the nerve roots are relatively less affected than those supplied by the posterior branches. An etiological or a pathogenetic relationship with diabetes is postulated for these reflexless areas.—S. W. Britton.

**The external activity of the pancreas and of the islets of Langerhans during hibernation** (*Activité exocrine du pancréas et îlots de Langerhans cas de l'hibernation*). Bierry, H. and M. Kollmann, *Compt. rend. Soc. de biol.* 99: 456. 1928.

In hibernating marmots the acinar portion of the pancreas atrophies, while the islet tissue does not seem to regress. This is associated with reduced sugar in the tissues and blood.—J. C. D.

**Is the endocrine function of the pancreas located solely in the islet tissue** (*La fonction endocrine du pancréas est-elle localisée uniquement dans les îlots de Langerhans*)? Bierry, H. and M. Kollmann, *Compt. rend. Soc. de biol.* 99: 459. 1928.

The arguments that the endocrine function of the pancreas is located solely in the islet tissue are based on the indirect proof that rabbits do not show glycosuria after the pancreatic duct has been tied and the acinar tissue allowed to degenerate, while the islet tissue remains intact. They are also based on the belief that in "angler fish," where the two tissues were supposed to be separate, extracts from the pure islet tissue yielded insulin and from the acinar tissue did not. The first argument loses its force, since rabbits fail to show glycosurea even after removal of the entire pancreas. The second is of no value, because careful histological study shows that the islet tissue is always too intimately associated with acinar tissue to permit a pure extract of islet tissue to be made. This point then still remains to be proved.—J. C. D.

**Diabetic acidosis: An etiologic factor in the production of auricular fibrillation.** Borg, J. F., *Minnesota Med.* 11: 580. 1928.

Attention is called to the rarity of consideration of acidosis as an etiologic factor in auricular fibrillation. A case is reported with such a relationship. Review of the literature reveals little mention of this relationship. The importance of attention to the heart as well as to the blood vessels in complications



of diabetes is stressed. The frequency of the occurrence of auricular fibrillation caused by diabetic acidosis, relieved by insulin, has made it seem advisable to call attention to its importance.—Author's summary.

**The effects of guanidine derivatives in diabetes (L'action des dérivés de la guanidine dans le diabète).** Castex, M. R. and M. Schteingart, *Compt. rend. Soc. de biol.* **99**: 999. 1928.

The guanidine derivatives, synthaline and glukhorment, were tested therapeutically on twenty-three diabetics. Both decreased the glycosuria and the hyperglycemia, and increased the carbohydrate tolerance in moderate and light cases. In severe cases they were not useful. In young subjects, whether well or diabetic, there was an intense glycosuria two hours after administration of glukhorment. This was present but less severe after synthaline.

**Emaciation and insulin. Hyperinsulinism.** Fonseca, F., *Arch. f. Verdauung-skr.* **42**: 362. 1928.

The author studied the gain in weight in diabetic patients taking insulin. The increase in weight the author attributes to the better utilization of food, thus better nutrition, and not to "insulin edema." He attacked the problem by measuring the water intake and urine output of these patients. The output exceeded greatly the intake, which would rule out any water retention, and in spite of this there was a marked gain in weight. The author suggests the opinion that in obesity cases we have to deal with the hyperfunction of the islands. The glucose tolerance curves in cases of Froelich syndrome and hypopituitary obesity suggest an insulin hyperfunction that the curve shows but a slight rise and the blood sugar values are low after the primary rise of the curve.—H. J. J.

**An electrocardiographic study of 123 cases of diabetes mellitus.** Hepburn, J. and D. Graham, *Am. J. Med. Sci.* **176**: 782. 1928.

Of the 123 cases, 56 showed serious electrocardiographic abnormalities at the beginning of treatment. When vascular disease with signs of cardiac failure was present at the beginning of diabetic treatment, the cardiac failure progressed in spite of the control of diabetes. However, in the cases without hypertension and no signs of cardiac failure, the abnormal electrocardiogram returned to normal in a large percentage of cases when the diabetes was controlled. Of the group (67 cases) with normal electrocardiograms only one of the 32 cases returning for a recheck had an abnormal electrocardiogram. This was in a patient requiring 60 units of insulin daily and who did not adhere to the treatment. The eradication of the foci of infection is important in preventing cardiovascular diseases. This is of extreme importance, as the chief cause of death in diabetes is vascular disease.—E. L.

**Diabetic therapy with special reference to the newer remedies.** Herold, A. A., *Ann. Int. Med.* **2**: 269. 1928.

Mention is made of intarvin, which was introduced by Max Kahn. The author believes that other factors are involved in cases of insulin-resistance. The use of synthalin may produce gastro-intestinal irritation. Judgment on "glukhormet" should be suspended until the question is settled as to whether it contains synthalin or not. Of the remedies from plants, jambul, Jerusalem artichoke and myrtillin have been used with some success.—E. L.

**A mechanism maintaining the hyperglycemia of diabetes.** Himwich, H. E., W. H. Chambers, Y. D. Koskoff, L. H. Nahum and M. A. Adams, *Proc. Soc. Exper. Biol. & Med.* **26**: 120. 1928.

It was previously shown that resting muscle of normal dogs may liberate lactic acid into the blood stream. The lactic acid may be removed by the liver and converted into carbohydrate. Fourteen fasted, depancreatized and diabetic dogs were used in the present work. Both during rest and exercise there was a greater concentration of lactic acid in the blood of the femoral vein than in that of the femoral artery. In acute experiments, in 16 of 22 observations, the

liver removed lactic acid from the blood, as judged by a considerably lower concentration in the hepatic than in the portal vein blood. Despite the hyperglycemia, in 18 of 22 observations the liver added glucose to the blood passing through it. The authors believe that this lactic acid glucose cycle is one of the mechanisms for maintaining hyperglycemia after the glycogen stores of the liver are reduced by fasting.—M. O. L.

**Hypoglycemic action of pancreatic extract given by mouth** (*Action hypoglycémiante dun extrait de pancréas administré per os*). Hornung, S., *Compt. rend. Soc. de biol.* 99: 1030. 1928.

Cats and dogs were tested with extract obtained by boiling the pancreas in alkaline solution. There was a certain amount of sugar reduction.—J. C. D.

**Action of "glukhorment" on normal dogs** (*Action du glukhorment sur le chien normal*). Hornung, S., *Compt. rend. Soc. de biol.* 99: 1031. 1928.

This was tested by feeding until the dogs died. There was a rapid fall in blood sugar, wasting and blood changes with cell damage in the kidneys and liver. The picture was the same as that produced by synthaline.—J. C. D.

**The hyperglycemic action of blood from a diabetic dog. Results of transfusion of diabetic and normal blood into animals carrying a pancreatic graft** (*Sur l'action hyperglycémiante du sang de chien diabétique. Les effets de la transfusion du sang diabétique et du sang normal chez les animaux porteurs d'une greffe pancréatique*). Kepinov, L. and S. Petit-Dutaillis, *Compt. rend. Soc. de biol.* 99: 481. 1928.

A dog was depancreatized and given a pancreatic graft just large enough to keep his blood sugar normal. Blood from a diabetic dog, when injected into such a test animal, caused a marked rise in blood sugar lasting several days. Blood from normal dogs did not give this rise. This is further proof of a sugar raising substance in the blood of diabetics.—J. C. D.

**Method of extracting the hyperglycemia producing substance from diabetic blood** (*Essai d'extraction des substances hyperglycémiantes du sang diabétique*). Kepinov, L. and S. Petit-Dutaillis, *Compt. rend. Soc. de biol.* 99: 484. 1928.

Blood is mixed with sodium fluoride, centrifuged, and the plasma decanted. It is then dialyzed through collodion. The dialysate is concentrated, freed from sugar, and dried. It is then extracted with alcohol, the extract dried and re-extracted. This final extract is freed from alcohol and redissolved in physiological salt solution. When injected, it produces the same increase in blood sugar in a dog with the minimum physiological amount of pancreas, as does blood from a diabetic dog.—J. C. D.

**The sensitiveness of the higher nervous centers to sugar during experimental pancreatic diabetes** (*Glycosensibilité des centres nerveux supérieurs au cours du diabète pancréatique expérimental*). LaBarre, J., *Compt. rend. Soc. de biol.* 99: 1053. 1928.

In addition to the direct effect on the endocrine system, the hyperglycemia of diabetes influences the higher centers which in turn stimulate the production of insulin by the pancreas. This was shown by three experiments with controls. Dog A was depancreatized. By carotid juglar anastomosis his blood was sent through the higher centers of dog B, whose head was connected to his body by the vagi only. The pancreatic vein of dog B was connected to the juglar of dog C, the registering animal, which had been previously decapsulated to make him insulin sensitive. High blood sugar through the head of B resulted in low blood sugar in C, i. e., active insulin secretion on the part of B. Normal blood sugar in B's cerebral circulation resulted in no such change.  
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**Insulin and the external secretion of the pancreas** (*Insuline et sécrétion externe du pancréas*). LaBarre, J. and P. Destrée, *Compt. rend. Soc. de biol.* 98: 1237. 1928.

In dogs, the higher nerve centers react to insulin and produce through the vagus a diminution in the external secretion of the pancreas. This involves all of the normal constituents of the secretion and is most marked when the hypoglycemia is at its maximum.—J. C. D.

**Two cases of haematuria caused by insulin treatment.** Lawrence, R. D. and A. S. Hollins, *Brit. M. J.* 1: 977. 1928.

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**Observations on the effects of substances other than carbohydrate in relieving the toxic symptoms of insulin.** Selman, J. J. and S. F. Weinman, *Am. J. M. Sci.* 176: 865. 1928.

Six cases of insulin overdosage which were treated with substances other than carbohydrate were considered. The first patient was given the whites of two eggs when the symptoms of insulin overdosage were present. The patient was relieved and there was a slight increase in the blood sugar. In the other five cases of insulin overdosage, 2-3 ounces of mineral oil were given orally. Four of these patient were relieved of their symptoms, though there were no appreciable increases in the blood sugar. One patient was not benefited by mineral oil.—E. L.

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Of seven subjects with malnutrition treated with insulin, all showed increased appetite and some had intense food craving following insulin; five showed definite gains in weight in response to insulin; one showed no gain whatever, but was slightly under the original weight at the end of three weeks; one was not observed a sufficient length of time. It is concluded that insulin can be a valuable agent for increasing weight in malnutrition. Attempts should be made to increase the fatty as well as the starchy foods after the administration of insulin when malnutrition is treated. Thirty minutes should elapse after insulin administration before food is taken, if the optimum development of appetite is desired. The insulin should be given three times a day before meals in doses of 10 units more or less, according to individual indications.—Author's summary.

**Insulin and metabolism of mineral salts (Pankreashormon und Mineralstoffwechsel. II. Mitteilung.)** Takeuchi, S., *Tohoku J. Exper. Med.* 11: 327. 1928.

Administration of insulin produces in the blood of normal dogs a decrease of sugar, inorganic phosphorus, potassium and calcium; a tendency toward increase of chlorine and serum-albumin; but no noteworthy change of sodium and magnesium. In the blood of dogs with pancreatic diabetes insulin produces a decrease of sugar, inorganic phosphorus, potassium and calcium; an increase of chlorine and serum-albumin; a tendency to increase of sodium; and no marked change of magnesium.—J. M. Connolly.

liver removed lactic acid from the blood, as judged by a considerably lower concentration in the hepatic than in the portal vein blood. Despite the hyperglycemia, in 18 of 22 observations the liver added glucose to the blood passing through it. The authors believe that this lactic acid glucose cycle is one of the mechanisms for maintaining hyperglycemia after the glycogen stores of the liver are reduced by fasting.—M. O. L.

**Hypoglycemic action of pancreatic extract given by mouth** (*Action hypoglycémiant du sang de pancréas administré per os*). Hornung, S., *Compt. rend. Soc. de biol.* 99: 1030. 1928.

Cats and dogs were tested with extract obtained by boiling the pancreas in alkaline solution. There was a certain amount of sugar reduction.—J. C. D.

**Action of "glukhorment" on normal dogs** (*Action du glukhorment sur le chien normal*). Hornung, S., *Compt. rend. Soc. de biol.* 99: 1031. 1928.

This was tested by feeding until the dogs died. There was a rapid fall in blood sugar, wasting and blood changes with cell damage in the kidneys and liver. The picture was the same as that produced by synthaline.—J. C. D.

**The hyperglycemic action of blood from a diabetic dog. Results of transfusion of diabetic and normal blood into animals carrying a pancreatic graft** (*Sur l'action hyperglycémiant du sang de chien diabétique. Les effets de la transfusion du sang diabétique et du sang normal chez les animaux porteurs d'une greffe pancréatique*). Kepinov, L. and S. Petit-Dutaillis, *Compt. rend. Soc. de biol.* 99: 481. 1928.

A dog was depancreatized and given a pancreatic graft just large enough to keep his blood sugar normal. Blood from a diabetic dog, when injected into such a test animal, caused a marked rise in blood sugar lasting several days. Blood from normal dogs did not give this rise. This is further proof of a sugar raising substance in the blood of diabetics.—J. C. D.

**Method of extracting the hyperglycemia producing substance from diabetic blood** (*Essai d'extraction des substances hyperglycémiantes du sang diabétique*). Kepinov, L. and S. Petit-Dutaillies, *Compt. rend. Soc. de biol.* 99: 484. 1928.

Blood is mixed with sodium fluoride, centrifuged, and the plasma decanted. It is then dialyzed through collodion. The dialysate is concentrated, freed from sugar, and dried. It is then extracted with alcohol, the extract dried and re-extracted. This final extract is freed from alcohol and redissolved in physiological salt solution. When injected, it produces the same increase in blood sugar in a dog with the minimum physiological amount of pancreas, as does blood from a diabetic dog.—J. C. D.

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**The thyroid and the rate of cell division.** Butler, E. G., *Proc. Soc. Exper. Biol. & Med.* 26: 231. 1928.

The effect of thyroxine solutions of various concentrations on the cleavage rate of *Arbacia* eggs was studied. Thyroxine in sea water in a concentration of 1:50,000 retarded the formation of the first cleavage furrow about 5 minutes. This retardation persisted through later cleavage stages. With a thyroxine concentration of 1:100,000 a lesser degree of retardation occurred. In thyroxine solution of 1:25,000 the reduction in rate of division was about twice that produced by the 1:50,000 solution.—M. O. L.

**Effect of infra-red radiation on growth of rachitic rat.** Clausen, Ethel M. Luce, *Proc. Soc. Exper. Biol. & Med.* 26: 77. 1928.

In young rats fed upon a rickets-producing diet, daily 10 minute exposures to near infra-red radiation caused an increased growth of the animal and prolonged their survival 4 to 6 weeks. This growth promoting effect was found to be associated with marked enlargement and hypertrophy of the thyroid gland, which was prevented by ultra-violet radiation. Some hyperplasia of the parathyroids was noted in rats under infra-red radiation.—M. O. L.

**Further experiments in feeding thyroid to fowls.** Cole, L. J. and F. B. Hutt, *Poultry Science*, 8: 60. 1928.

The results were in general confirmatory of earlier observations. Raw thyroid acted like desiccated thyroid, inducing hen feathering in male fowls, though having a less stimulating effect on feather growth. A daily dosage of 59 mgm. per pound of live weight hastened the normal moult of yearling hens, but had no appreciable effect on body weight or egg production. The feather structure in Sebright males (hen-feathered) was not affected, nor was there an appreciable lack of pigmentation in new feathers, such as had been noted by other observers after larger dosages. In silver Wyandotte males, feathers plucked from wing bow and saddle were replaced by feathers that, both structurally and in color pattern, conformed to the female type. New neck feathers, female in structure, tended toward solid black pigmentation.

**Reaction of thyroid gland to infections in other parts of body.** Cole, W. H. and N. A. Womack, *J. A. M.* 92: 453. 1929. *Abst., A. M. A.*

Further work done by Cole and Womack, on the relation of infections and toxemias to the histologic picture of the thyroid gland confirms their observations concerning the production of hyperplasia, loss of colloid, desquamation and decrease in iodine content in certain septic processes and toxemias. Somewhat similar observations have been recorded by other workers. The authors have developed a toxin containing a group of four organisms which, when injected subcutaneously into dogs, will produce these changes in practically 100 per cent of the animals if iodine has not been ingested by them. The average iodine content of the thyroid of normal dogs is 0.304 mgm. per kilogram of body weight, whereas the average iodine content of the thyroid glands of animals dying from severe infections is 0.142 mgm. per kgm. of body weight. Similar changes have been observed in the thyroid glands of human beings who have succumbed to acute infections, but these changes are present to a lesser degree. Evidence points to a relation of infections to hyperplastic glands in human beings. Basal metabolic studies made by the authors on animals with hyperplastic glands produced by toxemias and infections have revealed a basal metabolic rate elevated out of proportion to the fever. Injection of toxic doses of histamine produces a marked rise in the metabolic rate, without a significant rise in temperature, and also creates a desquamation, loss of colloid, decrease in iodine content and beginning hyperplasia in the thyroid gland. Injection of toxic doses of an amino-acid (glycocoll) produces the same histologic changes. The pathologic changes already mentioned in the thyroid as produced by infections can be prevented to a great extent by the oral administration of iodine. The data assembled support the theory that the thyroid gland takes an active part in the resistance of the body against certain toxins and infections. In spite of the added information that iodine exerts a protective rôle in the attack on the thyroid by infections, the authors still feel reluctant to advise the therapeutic administration of iodine to human beings suffering from severe infections.

**Adenoma and cancer of the thyroid.** Coller, F. A., J. A. M. A. 92: 457. 1929.

In a study of goiters from a severe goiter area, ninety malignant epithelial neoplasms of the thyroid were found, comprising 4% of all endemic goiters. A history of pre-existing goiter was present in 75%, but microscopic examination showed evidence of its origin from some type of endemic goiter in all except one instance. This exception arose from the hyperplastic gland of exophthalmic goiter. Of the patients, 72.2% were female and 27.8% were male, the same ratio that exists in the total number with endemic goiters. The ages varied between 14 and 72, with 34% occurring before 40 and 56% between the ages of 40 and 60. The chief leading symptoms were those associated with hyperthyroidism; next in frequency were pressure symptoms, while rapid growth was noted in only 15%. Of those examined, 46% had an abnormally high basal metabolic rate. Correct preoperative diagnosis was made in only 25%, while in 47% the diagnosis was unsuspected. Histologically, 28% of the growths were medullary carcinoma, 66% adenocarcinoma and 5.5% scirrhous carcinoma. A large number of adenocarcinomas were confined to adenomas. These should be considered true early carcinomas of the thyroid. Adenoma of the thyroid is a precancerous lesion with a small but definite incidence.—Author's summary.

**On the synthetic thyroxin, pharmacological experiments (Su la Tiroxina sintetica Esperienze farmacologiche).** Coronedi, G., Boll. d. Soc. di biol. sper. 8: 567. 1928.

Synthetic thyroxin was administered subcutaneously or intravenously to thyro-parathyroidectomized dogs and rabbits. The results indicated that there was a temporary return of vagus irritability, which had decreased after thyro-parathyroidectomy.—G. V.

**Operative treatment of exophthalmic and toxic goiter.** Kennedy, D., Practitioner, 121: 53. 1928.

If the removal of the excess thyroid tissue is regarded as a major operation and precautions taken accordingly, the risks are not any greater than in other major operations, popular belief notwithstanding.—A. T. C.

**Bacterial factor in goiter.** Houda, E., Northwest Med. 27: 240. 1928. Bacteria from goiter tissues; bacteriologic technic for their cultivation. Id. 348.

The author believes that there is a bacterial factor in goiters of all types. In cultures from 300 goiters, a Gram positive coccus organism was found, regardless of the type of goiter. Bacteria morphologically identical with those cultivated from goiter tissues have been cultivated from creek and river waters. The responses to the use of Lugol's solution may be explained on the basis of the action of iodine on the bacterial cause.—Author's Abst.

**Tetany and blood calcium after thyro-parathyroidectomy in the goat.** Larson, E. and L. A. El Gourie, Proc. Soc. Exper. Biol. & Med. 26: 210. 1928.

In the goat the usual operation for removal of the thyroids and parathyroids does not result in tetany. Tetany does not supervene because the goat can maintain a normal or nearly normal blood calcium.—Author's summary.

**The mechanism of secretion in the thyroid gland.** Ludford, R. J. and W. Cramer, Proc. Roy. Soc. B. 104: 28. 1928.

The authors have made a cytological study of the functional activity of the thyroid gland and of exophthalmic goiter. Droplets of secretion in the normal thyroid gland first appear in contact with the Golgi apparatus and pass out in the cytoplasm toward the lumen. Under the conditions of their study no reversal of polarity was observed. In the normal thyroid the secretion is discharged into the lumen of a vesicle and then absorbed into the blood stream. In human exophthalmic goiter there is a considerable enlargement of the mitochondria and of the Golgi apparatus. Both of these changes signify increased

secretory activity. The secretion droplets which are formed in association with the Golgi apparatus, which is reversed in this condition, discharge directly into the blood capillaries. The difference between the pathological and normal state is not merely an increased secretion of thyroid hormone, but an increased secretion of a different hormone due to the deviation of the mechanism of secretion.—E. L.

**Life curve of thyroid gland in goiter territory and in locality free from goiter** (*Zur Lebenskurve der Schilddrüse im Kropfland und in Kropffreier Gegend*). H. May, Arch. f. klin. Chir. 149: 501. 1928.

Basing his study upon an examination of specimens of thyroid tissue from 161 subjects in goiter districts and 179 subjects in goiter-free districts in Germany, the author attempted to decide upon what histological factor a comparative life curve of the thyroid gland can be based. The method of calculating the measurement of the follicles alone is regarded as faulty since it deals with but one component of the histological picture. Quite as important a factor is proliferation of cellular structures. In the thyroids of goiter-free districts the proliferation is by no means as great as that in the thyroids of goiter districts. The thyroid with the strongest growth tendency is that in which the follicles have marked proliferation. In direct contrast, the thyroid of the newborn presents no infolding of follicles. Between these two extremes nine stages are described in this study, in which the width of follicles, colloid filling, presence of proliferations, and number and intensity of the latter, indicate a basis upon which the life curve of the thyroid can be determined. It was found that the thyroid growth at puberty in goiterous as well as in goiter-free districts is more active and occurs earlier in the female than in the male. The thyroid of the male in goiterous as well as in goiter-free districts shows, after the sixtieth year of life, a renewed growth which is apparently absent in the female.—I. B.

**Iodine in Maryland waters in relation to goiter.** McClendon, J. F. and J. R. Sanford, Proc. Soc. Exper. Biol. & Med. 26: 263. 1928.

Goiter is prevalent in the mountainous region of western Maryland, and has a low incidence in the tidewater region. The authors believe that this is accounted for by the low iodine content of the drinking water of the western counties as compared with that of the seaboard.—M. O. L.

**A study on the antitryptic power of serum as a control of experimental athyreosis.** Preobrashensky, A. P. and E. P. Chernosatouska, Vestnik Endocrinology, 5: 341. 1927.

The authors examined the antitryptic power of the serum of 29 normal sheep and goats and of 28 thyroidectomized sheep and goats by the Grass-Field method. As the antitryptic unit, they considered the least amount necessary to neutralize the amount of trypsin which can digest 7.0 cc. of 0.1% solution of casein at 50° C. in 30 minutes. The authors arrived at the following conclusions: The content of antitrypsin in the serum of normal sheep is 4800-84,000 AE. per cc. and 19,200-20,400 in one cc. in goats; the content of antitrypsin in serum of thyroidectomized animals is reduced to 41% in sheep and 63% in goats; if the thyroidectomy was not complete the antitrypsin of the serum was almost normal.—Olga Sitchevskaya.

**Effect of diathermy of the thyroid gland on basal metabolism** (*Influence de la diathermie de la glande thyroïde sur le métabolisme basal*). Ptaszek, L. and M. Szuperski, Compt. rend, Soc. de biol, 99: 1028. 1928.

In hyperthyroid cases diathermy reduces the basal metabolism markedly. In hypothyroid cases it raises it, while in normal cases it has little effect. The duration of these changes is not noted.—J. C. D.



# ENDOCRINOLOGY

## THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

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### ENDOCRINE REGULATION OF REPRODUCTION\*

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COLD SPRING HARBOR, N. Y.

It is evident that "endocrine regulation of reproduction" is not the subject of a single investigation. It is presented as a standpoint, or conception, of considerable consequence in viewing facts which fall into several chapters of present and future knowledge of the internal secretions. It is a conception that could have arisen only after a generation of revealing and revolutionizing study. Indeed many investigators will doubtless consider this conception premature or ill-founded even now. But probably all will agree that a point of high importance to the whole subject of internal secretion will have been attained whenever it can be shown that one major section of animal organization is largely divorced from control by nerves, and is found to be fully guarded and efficiently controlled by hormones. If, or when, it is found that the mechanism of reproduction in higher animals and man are under the control of the endocrine system, not of the nerves, we may have obtained the key to the special significance of hormones in animal organization. If it is true that in the various, complicated and rhythmic mechanisms of reproduction in higher animals the nervous system has notably failed to impress itself with its usual degree of control, and if endocrine control has proved especially effective in regulating these same highly rhythmic processes, we shall have extracted a deeper meaning of the endocrine organs in the origin and evolution of higher animals.

Two years ago the writer (1927) expressed the opinion that the known facts support and warrant this general conception of these organs. At the present moment, better than at any previous time, the full strength of this view can be presented. For this reason we here undertake to add a supplementary statement to our earlier and quite different treatment of this subject.

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\*Presidential address at the Thirteenth Annual Meeting of the Association for the Study of Internal Secretions, Portland, Ore., July 9, 1929.

REPRODUCTIVE MECHANISMS SEEM NOT TO BE UNDER CONTROL OF THE  
NERVOUS SYSTEM.

The story of the rôle of the nervous system in reproduction, as we now know it, is short and doubtless incomplete. Several years ago, in collaboration with King (1921), we obtained some evidence—we concede it is not conclusive—that at least the final stages of secretion or laying down of albumen and shell on the eggs of birds is not under the control of the nervous system. The bird's oviduct, or uterus, apparently receives sympathetic and parasympathetic innervation; but nerve block—by means of nicotine, atropine and cocaine, or nerve stimulation by pilocarpine—has little or no effect on the secretion of these egg-envelopes. The conclusion drawn in 1921 was that “the meager modification of the amount of albumen and shell secretion obtained by us by means of drugs with presumably pronounced action upon the nerve supply of the oviduct thus affords some evidence that . . . this mechanism is little if at all directly affected by nerve action.”

The most significant fact now available on this part of our subject is contained in a very recent preliminary statement by Cannon (1929). From his short published abstract it appears that Cannon has been able to show that, following complete bilateral sympathectomy, female cats can continue to perform the functions of reproduction. Since the generative organs of mammals are so largely innervated from the autonomic system this result would appear to come near to a demonstration that the specialized reproductive functions are essentially independent of nervous control. In this statement we do not mean to suggest that a nerve supply is without significance in the embryological development of these organs; nor that it has no trophic value to reproductive tissues; nor that nerve and mental elements fail to enter such acts as copulation; nor yet that nervous disorder is unable completely to inhibit or destroy the capacity to reproduce.

A further fact of interest to this subject is perhaps to be found in the independence of mental and sexual development in cases of puberty praecox. Gesell (1928) has recently published the results of psychometric tests (extending over periods of four and five years) made on two such subjects—one of which began regular menstruation at the age of 3 years, 7 months. From the prolonged study of these two cases the conclusion is drawn that “the general course of mental maturation is only slightly perturbed (and this chiefly on the emotional side) by the precocious onset of pubescence.” Of course, it is conceivable that the central nervous system (recent studies, however, assign this function to the anterior pituitary), could influence this precocious development of the reproductive system, even though the reverse or reciprocal action is impossible. Nevertheless, the measurements which have shown that such precocious development and partial functioning of the reproductive apparatus leaves mental development essentially untouched are of some significance here.

These few facts must constitute our entire discussion of the question of nervous control of reproduction. Any additional facts known to others should be placed in evidence, and a further investigation of this problem is greatly needed. But the facts just reviewed plainly indicate that the essential processes of reproduction, as these occur in birds and mammals, are not under the control of the nervous system. That nerves may modify the rate at which some hormones are secreted, and that some nerves are affected by the altered amounts of these secretions, are points of no immediate concern to this discussion.

#### RELATIONSHIP OF INTERNAL SECRETIONS TO REPRODUCTION.

Several of the endocrine organs are so closely and primarily identified with reproduction that they need merely be mentioned here. The testis, ovary, corpus luteum and placenta leave no doubt of their primary relationship to reproduction. Other organs which are in a somewhat different category, because they affect other processes in addition to reproduction, are the anterior pituitary, suprarenal and thyroid; but everyone concedes that these organs are related to reproduction. Some investigators also assign to the pineal only sexual and reproductive functions. Everyone grants to the posterior pituitary at least a minor rôle in reproduction through its action on uterine muscle. But to most investigators the pancreas, thymus and parathyroid seem quite unrelated to reproduction. Using the bird as our test animal—this being a form which still retains the type of reproduction prevalent in all vertebrates except mammals—we think our own studies have disclosed good evidence that even these three last-named organs (pancreas, thymus and parathyroid) are important regulators of processes of reproduction. To point out this evidence for these three organs, and to review evidence from the bird world showing that still other endocrine organs have a larger share in reproduction than is usually conceded to them, is our further task and purpose here.

*Seasonal size changes in endocrine organs associated with seasonal changes in reproduction.* In doves and pigeons it has been possible to observe that seasonal changes in size or function occur in several endocrine organs closely coincident with seasonal changes in reproduction. These cases therefore display a new or little recognized relationship of endocrine organs to reproduction. In Fig. 1 are brought together the changes observed in seven organs. The liver, spleen and intestine are here included because of their rather special association with endocrine organs. In examining these diagrams—which picture seasonal size differences only and not the full size of the organs—it may be recalled that such a series of seasonal changes has thus far been worked out for no other animal, not even for man. Again, since seasonal reproductive periods are absent in man and many mammals it is less convenient to study these relationships in mammals. The data for the thyroid show it to be largest in winter and autumn, smallest in spring and summer. The gonads, both testis and ovary, show seasonal changes of directly opposite nature. The data on blood calcium

## REGULATION OF REPRODUCTION

(interpreted as parathyroid activity) is known for three of the four seasons. Its change is directly opposite that of the thyroid but parallel to that of testis and ovary. The spleen and liver, like parathyroid, testis and ovary, all show highest weight during the period of maximum reproductive activity—a period coincident with smallest thyroid weight and

## SEASONAL SIZE CHANGES IN ENDOCRINE ORGANS

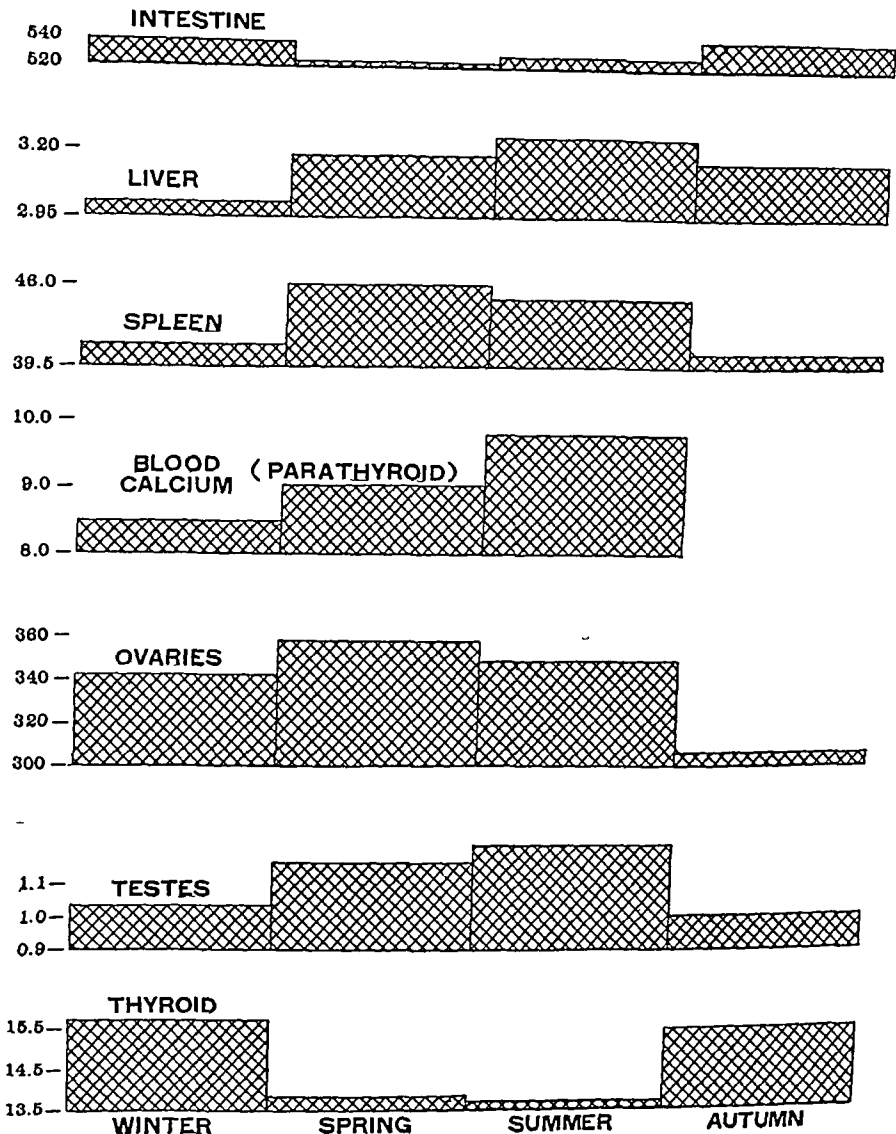


Fig. 1. Seasonal differences in endocrine and associated organs in ring doves. The numerals (at left) express quantities of organ: Thyroid, ovary and spleen (absolute weight in mgms.); testis and liver (weight in grams); blood calcium (mgms. per 100 cc. of blood); intestine (length in mm.).

lowest thyroid function. The two periods of largest thyroid size and activity are the periods of smallest size in all of the other five organs thus far mentioned. The point of particular interest here is that the spring and summer periods are the periods of *active reproduction*. Exposed to full winter conditions, when the thyroid is largest and most functional,

reproduction is entirely suppressed in these animals (in our practise, winter conditions are mitigated and diminished reproduction may occur). But when thyroid weight is low, or rather while it is undergoing a definite decline in weight and function, the period of riotous reproduction occurs in these animals.

The fact that liver and spleen both enlarge during the period of active reproduction raises the following question: Are these two enlargements to be considered merely as parts of a generalized splanchnomegaly due to increased activity of the anterior pituitary during the period of active reproduction? In order to obtain some information on this possibility we have included some data on intestinal length. There are special reasons for expecting an increase of intestinal length as a result of a hyperactive pituitary gland. Stated otherwise, a change in intestinal length should supply evidence for a seasonal change in pituitary size. It will be observed, however, that the available data (sex means for 600 healthy doves) show little or no change of intestinal length with season; and the indicated direction of change (probably not statistically significant) is opposed to that in liver and spleen. We consider these data on intestinal length significant only in that they indicate that the seasonal changes in liver and spleen are not aspects of a generalized splanchnomegaly; and that, in this material, an evidence for seasonal change in the activity of the anterior pituitary is now lacking. It should be noted, however, that in the majority of these birds reproduction was not entirely suppressed—but merely diminished—in autumn and winter. Animals which show a more restricted breeding season might better reflect, by a change in intestinal length, possible variations of pituitary activity in association with the reproductive cycle.

As a result of this examination of seasonal changes of size and function in endocrine organs it is found that thyroid and parathyroid bear a relation to reproduction that has been elsewhere quite generally overlooked. The seasonal size differences that occur in liver and spleen probably reflect the action of a number of endocrine organs—all closely synchronized with the period of active reproduction. This probable association is further emphasized by the fact that the liver and spleen show a sex difference in size (Riddle, 1928), as does also the intestine and pituitary (Riddle and Flemion, 1928.)

*Temporary changes in blood and endocrine organs in synchrony with each ovulation period.* We may now briefly consider a series of blood and endocrine changes which have been found to occur coincident with every ovulation period in the pigeon. The time at which an ovum or yolk leaves the ovary marks the culmination, or maximum expression, of the following endocrine changes: The production of ovarian or follicular hormone, as indicated by oviducal growth; the hypertrophy of the suprarenals; the increase of blood sugar; the activity of the parathyroids, as measured by the blood calcium—an observation which has since been duplicated in fishes by Hess and coworkers (1928). The time (108 hours earlier) when such

ova begin their period of rapid growth is the time when all the above-mentioned things begin to increase, and also the time at which the amount of blood fat and of lipid blood phosphorus begin to increase.

To the above-mentioned changes, more fully described in a previous publication (Riddle, 1929), we are now able to add another. During

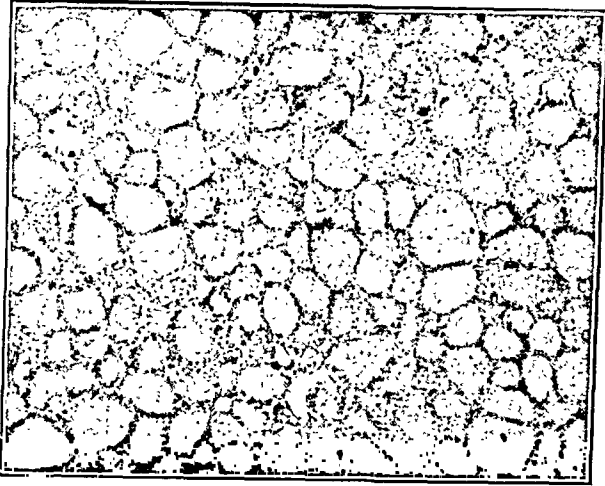


Fig. 2. Thyroid structure typical of the "resting" thyroid (more than 108 hours removed from ovulation) of the pigeon.

recent months, Dr. Krizenecky, working in our laboratory, has shown that the histological picture of the pigeon's thyroid undergoes characteristic changes with each of these ovulation cycles. The complete story for the several parts of the reproductive cycle will be reported later. Meanwhile,

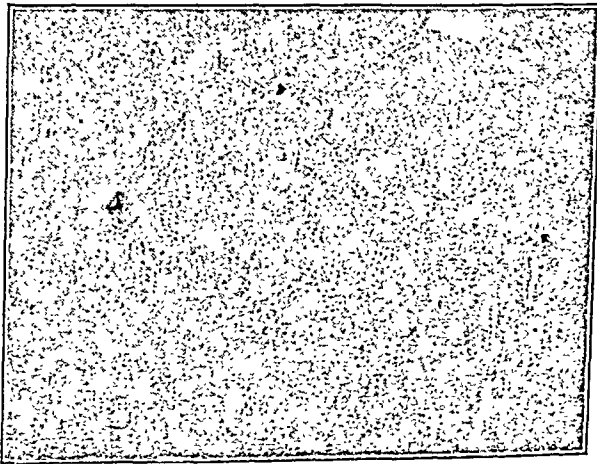


Fig. 3. Thyroid structure considered typical of the time of dehiscence (ovulation) of an ovum from the ovary of the pigeon.

eliminating consideration of a confusing type of hyperplastic thyroid which is not rarely found in this material, the differences between the "resting" thyroid and that of the thyroid "at ovulation" (only 108 hours later) are reproduced in Figs. 2 and 3. For our present purpose we need only observe that the thyroid, like the other endocrine organs cited above,

plainly and notably responds to the various phases of each reproductive cycle. Ten to forty such cycles may occur during each year of the reproductive life of these animals.

We have noted that the blood sugar is increased at and near every period of ovulation in the pigeon. A similar increase of the blood sugar, persisting for a few weeks, was earlier observed by Scott and Kleitman (1921) at the single annual ovulation period in the frog. Since in pigeons this glycaemia seems invariably to accompany ovulation it was thought well to find out whether the final growth and dehiscence of ova from the ovary could be prevented by keeping the blood sugar low by means of insulin. It was found that moderate dosage, given twice daily to 10 females during one month, suppressed 90 per cent of the ovulations that should have occurred during this period. Though these results do not show that the incretion of the pancreas is definitely related to reproduction, they suggest that the islets do not combat—or at any rate they do not successfully combat—the glycaemia of ovulation, though this glycemia persists in the bird for a total of at least 6 days. To this extent the internal secretion of the pancreas seems to share in the processes of vertebrate reproduction.

The data thus briefly discussed take us into the midst of a wide variety of fine adjustments effected by internal secretions to meet one single phase of reproduction. The whole of the reproductive cycle is a remarkable sequence of such phases, and as we turn to a momentary examination of some of these we here also find the internal secretions much in the foreground.

*Other observations.* We have earlier reported (Riddle, 1924, 1929) that the thymus is related to the capacity of most vertebrate animals to secrete the egg envelopes which they place around their eggs. It is certain that desiccated ox thymus has a specific capacity to restore this function to certain birds which have lost this function. Some experiments now in progress in our laboratory have, however, clearly indicated the difficulty of obtaining defective egg-envelopes by an early and apparently complete thymectomy of the pigeon—even when this is accompanied by the removal of the bursa Fabricius, which some authors consider an accessory or cloacal thymus. Our tests on this matter are still under way, and it is quite possible that some of my earlier expressed views concerning this troublesome organ must be revised. Nevertheless, as noted above, the thymus certainly bears a special relation to the secretion of these egg-envelopes. In birds at least the thymus also certainly bears a special relation to the period of body and gonad growth, and to the time of attainment of sexual maturity (Riddle, 1928a).

Thus when we look into the mechanisms of reproduction as these occur in the vertebrates which have furnished the foundation for the reproductive system of the mammal, we can indeed find relationships of parathyroid, pancreas and thymus to reproduction. Among the substances generally accepted as vertebrate hormones it is only in the case of secretion that no

relationship to reproduction can be claimed. And in this isolated case we find the hormone definitely related to a highly rhythmic function—a function as rhythmic as that of reproduction.

The rôle of the anterior pituitary in hastening sexual maturity—in the initiation of reproductive power—is of very recent demonstration but is now too well known to require comment here. Accelerated gonad growth under its influence has been observed in both mammals and birds. These facts, like the histological changes of the gland in pregnant mammals, closely associate this gland with a share in the guidance and control of reproduction. The numerous facts, old and new, which show the relationship of the pituitary and suprarenal to sexuality or to reproduction are common knowledge and beyond the space limits of this paper.

Despite the multitude of publications dealing with this subject it is probable that we still have a very imperfect knowledge of the relationships of the thyroid to the several aspects of reproduction. Though the literature on these subjects is not entirely consistent it seems well to make the briefest reference to the effects of cretinism and hyperthyroidism on reproduction. Kunde, Carlson and Proud (1929) recently report that the daily administration of a small amount of thyroid is favorable to reproduction in cretin rabbits; also, that in severe experimentally induced hyperthyroidism the processes of oestrus, ovulation and implantation may occur, but in most instances the fetuses are resorbed. Hoskins (1910) had earlier noted that abortions were frequent in guinea pigs given larger doses of desiccated thyroid. One can not review the results of clinical and experimental studies without considering it probable that more than one type of sterility is primarily of thyroid origin.

#### SUMMARY

In a summary view of this subject it appears that nearly all of the internal secretions are intimately concerned in one or another special aspect of reproduction. Where this is not true in mammals it is nevertheless true in the ancestral vertebrates from which the mammals were derived. Again, the only hormone now recognized as having originated within the mammalian group—the corpus luteum—is related solely to reproduction; associated with this is the interesting fact that structurally the mammal differs more from its immediate ancestors in its reproductive system than in any other organ system. One vertebrate hormone—secretin—is not concerned with reproduction, but regulates a process as highly rhythmic as is reproduction.

Our knowledge of the rôle of the nervous system in reproduction is not wholly conclusive and requires further investigation. The facts now known indicate that the essential aspects of the mechanism of reproduction are not under the direct or immediate control of nerves.

It appears therefore that in large and complex organisms the nervous system has proved inadequate for the control of the elaborate mechanisms



of frequent and rhythmic reproduction. The organs of internal secretion have been found actually in control of precisely these same complex rhythmic processes. In view of the relatively greater share of the nerves in the control of other active organ systems it seems probable that the true hormones may now be best regarded as agents devised primarily for regulating activities and coordinations incident to essential and irregular rhythms. Of special significance among such rhythms, apparently, are the species-preserving rhythms of reproduction.

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# NASAL SPRAY METHOD OF ADMINISTERING HORMONES OF THE OVARY AND PITUITARY GLAND\*

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As is commonly known, the internal secretion of the ovaries and pituitary pass into the circulating blood almost continuously during the period of life in which these glands actively function. Even though there are cyclic variations in amount of secretion, activity of the glands is continuous. Accordingly, when it is indicated to use hormones from these glands therapeutically, a method of administration which approximates this natural continuity of supply is desirable. Consideration of the various methods of administration demonstrates many advantages for the nasal spray.

Hormones may be introduced into the blood stream directly by intravenous injection, or indirectly by intramuscular or subcutaneous injection. Absorption is rapid when either of these methods is used and the effect produced is correspondingly transitory. Either method will produce quick action, but to secure prolonged activity another means of application is preferable.

Absorption by mucous membranes is relatively slow and, therefore, a more prolonged action is assured. For the purpose of therapy in general, mucous membranes of the gastro-intestinal tract are more useful than other mucous membranes of the body. But experience has shown that the active principle of the thyroid is the only secretion which can be given by mouth with satisfaction. If the gastro-intestinal tract is excluded, the other mucous membranes available are those of the nose, eyes, or vagina. Any of these may serve to transmit a hormone into the blood stream, but the nasal mucosa seems to offer the most advantages.

That pituitrin may be administered successfully by nasal spray, has been demonstrated by Blumgart (1), who, in 1922, reported a case in which pituitrin absorbed by nasal mucosa alleviated the symptoms of diabetes insipidus. He stated that, "Extract of the posterior lobe applied intranasally checked both the polyuria and polydipsia as effectively as hypodermic injections."

The ordinary atomizer, which can be obtained at any drug store, may be adapted for the economic use of small amounts of pituitrin as reported by Kintner and Greene (2). They advocate the insertion of a small test tube in the atomizer bottle in such a manner that the suction tube of the

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atomizer nearly reaches the bottom of the test tube. They cite one case to compare the relative efficiency of pituitrin in controlling diabetes insipidus when the hormone is administered by hypodermic injection, nasal swab, or nasal spray. The nasal spray proved to be practically as efficient as either of the other two.

Although all obstetricians do not agree that pituitary extract is desirable and safe when used for the induction of labor, many do use it for this purpose. Hofbauer (3), who introduced this method of induction of labor, recommends nasal administration on cotton swabs which are placed in the nostrils. He calls attention to the reaction of the nasal mucosa which results in a coating of mucus forming around the nasal pledgets to such an extent that long continued absorption is prevented unless the pledgets are changed frequently. This being the case, it seems to us that when continued action is desired, the nasal spray is preferable to the cotton swab, for in this manner most of the local reaction is eliminated.

#### ANIMAL EXPERIMENTS

Since rats and mice give such a well defined reaction to ovarian hormone when injected hypodermically, we undertook to determine whether the same reaction could be obtained by absorption through the mucous membranes. Spayed mice were given ovarian hormone by means of cotton pledgets which were inserted into the vagina. Although these pledgets were saturated with the hormone, the changes in the vaginal mucosa characteristic of estrus were not seen after such application. The mucous membranes of the eyes and nose of mice were also treated by dropping the hormone on these membranes at frequent intervals during the day, but no definite reaction followed this procedure. Probably the amount absorbed was so small that all experiments with mice could give only negative results.

Rats proved to be better suited for these experiments, for when the saturated pledgets were left in the vagina for a few hours the characteristic change of estrus occurred. However, it was found that the smallest vaginal dose which gave a positive test was double the amount necessary to give the same result as occurred when the material was injected hypodermically. Positive results were also obtained when the hormone in a concentration of ten rat units per cc. were dropped into the eyes or nose. It is difficult to calculate the amount used in this manner, for if the drop were a little too large only a part of it would be retained. Then, too, the animal would frequently brush the eyes with its paw before absorption had taken place. However, when drops were applied to both eyes at three or four hour intervals for a period of twelve hours, characteristic changes of estrus would occur. No untoward results followed such administration. From the rat experiments, therefore, we concluded that vaginal mucosa, nasal mucosa, or conjunctiva could be safely used for administering ovarian hormone, and that the same results were obtained as followed hypodermic

injection, although more material must be used when applied to mucosa than by hypodermic injection.

#### MATERIAL

For clinical purposes a small glass nebulizer (Glaseptic) has been used because it is economical and convenient. However, any atomizer may be adapted as described by Kintner and Greene (2).

The ovarian hormone which we have used has been in concentration of ten rat units per cc. (Estrogen plain and specially scented, and Amniotin).<sup>\*</sup> Pitocin and Pitressin are the two active principles of posterior lobe extract<sup>†</sup> as described by Kamm et al (5).

#### ILLUSTRATIVE CLINICAL CASES

Among the clinical tests which have been made to determine the efficiency of nasal spray administration of hormones many have shown satisfactory results. The material used has been ovarian hormone, pituitrin, pitocin, and pitressin. A few illustrative cases are reported briefly here. The first case affords an excellent opportunity to compare nasal spray with hypodermic injection.

Miss A. C., age 34, who was reported on in 1926 (4), gave a history at that time of irregularity of menstruation for several years with intervals as long as six months to a year. She showed evidence of hypothyroidism and for that reason thyroid extract was given, with the result that regularity of menstruation returned and the menstrual flow came to be nearly normal in amount. This patient has been followed over a period of eight years, during which time she has received treatment with ovarian hormone for more than four years. The benefit derived from the hormone has been sufficient to cause her to come regularly for treatments. When the possibility of nasal sprays being administered at home was suggested she became quite enthusiastic, since this would eliminate frequent trips to the hospital to receive hypodermic injections. For the past year she has been taking ovarian hormone as a nasal spray, using ten rat units per day during the last two weeks of the intermenstruum. The results have been just as satisfactory as those obtained by hypodermic injection. The patient has been anxious to determine for herself as well as for us the importance of both the hormone and thyroid extract. Accordingly, various combinations have been tried, omitting the thyroid extract at one time, and omitting the ovarian hormone at another. The combination of the two is necessary to keep the patient menstruating normally. When either one is omitted the interval increases and the flow diminishes.

This case has been of special interest because of the opportunity to follow a single individual over a period of several years and to see so clearly demonstrated the favorable effects of the hormone when used regularly.

<sup>\*</sup>Estrogen has been supplied by Parke Davis & Co. Amniotin has been supplied by E. R. Squibb & Sons. <sup>†</sup>Pitocin and Pitressin have been supplied by Parke Davis & Co.

Another case which has been followed over a considerable period of time also demonstrates the value of ovarian hormone in scanty and irregular menstruation. This patient also was disturbed by frequent headaches and by the fact that she was sterile and lacked libido. The important findings on physical examination were overweight of thirty-five pounds, an excessive growth of hair on the face, all the genital organs were small as determined by pelvic examination, and her basal metabolic rate was plus or minus zero. She had menstruated first at fourteen and again one year later. From then until the age of twenty-five menstruation occurred very irregularly and, according to the patient's statement, "never twice alike." The intervals varied from three to six months and the period never lasted more than four days.

Two and one-half years ago treatment was begun with the administration of one-half grain of thyroid extract twice a day, which amount she has continued to take until the present time. A weight-reducing diet was prescribed with the result that in six months' time she reduced her weight to normal and has maintained that level since. At the same time the other treatment was begun. She was given injections of ovarian hormone, thirty rat units per day in two to four injections distributed as equally as possible throughout the twenty-four hours. These injections were continued for twenty days, at the end of which time the patient began to menstruate and flowed for four days. The hormone was discontinued for two weeks. Then the injections were repeated, in a similar manner, for the last two weeks of the intermenstruum in the second, third and sixth months. As a result of the combined treatment the patient has menstruated every month during the last two and one-half years and the interval has been approximately 28-30 days. The weight reduction was accomplished in the first six months and a constant weight has been maintained since. The amount of thyroid, one grain a day, has been constant throughout. The ovarian hormone was given on the first, second, third and sixth months, and then discontinued. For nine months menstruation was normal, then the flow became scant lasting three to four days. At this point the patient became alarmed and returned, requesting more of the hormone. Accordingly, injections were given for two weeks and a normal menstruation re-established for two months. When she returned later on account of scanty flow she was given the nasal spray with instructions to use ten rat units per day. She menstruated five days after the beginning of this treatment. The following month the same procedure was carried out and the patient menstruated four days with a much greater flow than had occurred in the past few months. She has continued to use ovarian hormone by nasal spray and normal menstruation occurs. It seems to have been demonstrated in this patient, therefore, that ovarian hormone is necessary to maintain her menstruation at normal intervals with normal amounts of flow. It is interesting to note that while the genital organs were small at the original examination, during the course of treatment they developed to an average size, and the patient's libido has returned.

These two cases serve to illustrate the use of ovarian hormone in this type of menstrual disturbance, i.e. scanty and irregular menstruation. It is in this group that the results with the hormone have proved most satisfactory. Many other cases have been treated with equally satisfactory results, though occasionally the results were negative. As reported in the previous work (4), the ovarian hormone has not been proved to be of any benefit in the natural or artificial menopause, for although a slight increase in size of the uterus occurs menstrual flow does not appear. In order to draw conclusions, one should follow a patient over a considerable period of time for, as illustrated by the following case, one could easily be misled by drawing conclusions too early.

Mrs. R. J., age 36 years, complained of amenorrhea of three years which began after curettage for retained membranes. She had tried many and various remedies without success but when thyroid extract and ovarian hormone were used for one month she menstruated normally. This occurrence was suggestive of the value of this form of therapy but with the continuance of the same treatment there has been no further menstruation for a period of several months. It is not reasonable to assume, therefore, that the ovarian hormone was any great factor in bringing about this single menstruation. If this patient had left our observation immediately after the one menstruation it would have been easy to assume that the therapy used had effected a re-establishment of menstruation.

The nasal spray has proved just as satisfactory for administration of pituitrin as it has for the ovarian hormone. One of the uses for pituitrin is illustrated by the following case:

Miss M. H., age 31, sought relief for profuse menstruation which proved to be due to numerous endometrial implants which involved both ovaries and also invaded the posterior wall of the uterus. Since she was anxious not to have menstruation cease, only a part of the ovarian tissue was removed at operation, and not any of the uterus was sacrificed. The patient preferred to take a chance on the necessity of a second operation rather than be assured of relief of symptoms by complete removal of pelvic organs. At the first menstruation following operation the flow was excessive but the amount of blood lost was not alarming. The second period began with a gush of blood, and real hemorrhage occurred so that it was necessary to use a pack to stop the flow, and the blood loss being so great that two transfusions were given. Although alarmed at the occurrence the patient was loath to part with the uterus. At the expected time for the next period she entered the hospital where she could be closely observed while remaining quietly in bed. At the onset of flow ergot was given by mouth and also pituitrin by nasal spray. In this manner the amount of flow was satisfactorily controlled so that the patient was greatly encouraged, and she believed a solution for her problem had been found. For the succeeding menstruation she used sufficient pituitrin by nasal sprays to control the amount of flow. Although she has reported regularly after each menstruation no other treatment than pituitrin administered by herself

has been necessary during the past year. The patient has demonstrated to herself that pituitrin by nasal spray will control what otherwise would be a dangerous uterine hemorrhage.

Pituitrin by nasal spray has been used for relief of symptoms of diabetes insipidus since first reported by Blumgart (1). Now that Kamm et al (5) have separated pituitrin into its two active principles of pitressin and pitocin, it is interesting to note that one of these, pitressin, is effective in controlling the symptoms of this disease and for this purpose does not seem to differ from the action of pituitrin. No untoward symptoms have been seen following its application to the nose.

The other principle, pitocin, is useful for stimulating uterine muscle. If quick action is needed as, e. g., to control hemorrhage in the third stage of labor, hypodermic injection is preferable. When a milder and more prolonged action is desired as in the induction of labor, nasal spray is more desirable than repeated injections.

There are some conditions in the uterus accompanied by a varying amount of continuous bleeding which respond well to pitocin by nasal spray. Some of these conditions are often characterized by the term chronic subinvolution which includes an enlarged uterus with poor muscle tone. This may be a part of a general condition or it may be due to uterine displacement with poor circulation. When a serious condition such as carcinoma or benign tumor can be excluded, nasal spray of pitocin often affords symptomatic relief. The amount of pitocin needed varies with the individual case. Small amounts frequently repeated are indicated in this group.

The following case illustrates how ovarian hormone and pitocin may be used as an aid in diagnosis. Miss E. R., age 22, complained of more or less continuous bleeding for the past two years. She never has had regular periods and recently she hardly knows when menstruation begins on account of the continuous bleeding. Pelvic examination revealed a rather large, soft uterus, with both ovaries larger than average. Treatment was begun with pitocin administered by the patient herself as a nasal spray, at home and at the office. This controlled the hemorrhage while it was being used. The pitocin was stopped and ovarian hormone substituted with the result that the uterine bleeding became excessive, so the ovarian hormone was stopped and the pitocin resumed with relief of symptoms. This led us to believe that the patient had a cystic hypertrophy of the endometrium with hyperfunction of the ovaries. She was unable to carry on the treatment while at work and insisted on more radical measures. Accordingly, the uterus was curetted and one ovary removed. The endometrium removed showed considerable hypertrophy with small cysts and folds. Neither ovary showed any evidence of a corpus luteum and the ovary which was removed had a thickened capsule and contained a large number of follicles. Although this condition was suspected before treatment was begun, the use of pitocin and ovarian hormone was a definite aid in making the preoperative diagnosis.

## DISCUSSION

When the hormone has been sprayed into the nose, all of the material appears to be absorbed and there has been no sign or symptom of local irritation. The method of administration is so simple that the patients have no difficulty in managing it at home. While there has been no complaint following the use of the plain hormone, some patients prefer a specially scented preparation.

When coryza or other local abnormality contraindicates application to the nasal mucosa, the vaginal mucosa or the conjunctiva may be used, but the administration by the conjunctiva is not practicable in the human subject. A few patients prefer that the application should be made to the vagina. The reason for this choice is usually psychological.

Frequently repeated doses, as can be administered by the patient, approximate normal conditions in a way that cannot easily be accomplished by hypodermic injection. Therefore this method increases the field of usefulness of the hormones.

The results obtained from our experimental and clinical tests indicate that the nasal spray administration of ovarian hormone, pituitrin, pitresin, and pitocin is efficient, easy, and safe.

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# STUDIES OF THE ENDOCRINE GLANDS

## VIII. The Differential Diagnosis of Endocrine Disorders

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### SECTION I

In an earlier communication (1), the author described in some detail an objective method for the differential diagnosis of disorders of the several endocrine glands and the separation of such endocrinopathies from the numerous non-endocrine conditions simulating them in their clinical and laboratory evidences. Later papers, in collaboration with Dr. C. H. Lawrence, have presented the results from the application of the method severally to functional disturbances of the pituitary (2), the thyroid (3), the gonads, male and female (4), the adrenals (5), and a group of so-called "pluriglandular" syndromes (6). A subsequent article (7a, b) has dealt with an analysis of a series of cases each of which offered clinical or laboratory evidence suggesting an endocrinopathy but which on thorough study gave positive evidence of an underlying etiology unassociated with the ductless glands.

The present communication is designed to amplify and summarize the earlier papers and present in as concrete and practical form as may be possible the results of experience gained in studies that have been actively carried on since 1912.

As the present series of cases from which these conclusions are drawn includes well over 4000 patients who have been thoroughly studied, the collation of material and its presentation in reasonably simple and compact form offers certain difficulties. While some of the data can be tabulated satisfactorily, much of the material cannot be. Variations in the functional level of a single gland often fail to produce correspondingly varying changes in many of the objective data. A further complication lies in the variable relationships of such composite glands as the pituitary and the adrenals. All of these factors lead to end results that in the summation of a general series may be mutually compensatory and so yield figures the apparent normal level of which is wholly misleading. The marked deviation from normal performance shown in the individual case is thus obscured and its true significance lost.

To summarize the complete picture of each gland as a separate entity would defeat the present purpose. Each point would require discussion on the basis of comparison and contrast with all of the glands as the method is essentially one of differentiation. This could only mean a wearying duplication.

On the whole, it has seemed best in presenting the material to follow the actual method of practice, making running comment on such points as have an actual significance or a possible suggestion. In the interest of simplicity, also but scanty reference will be made to the existing diffuse endocrine literature. Citations will be made from the papers in the series of which this is the summary, but solely because they are expository to the text. The basis for inclusion of the few remaining references will be apparent from the context.

As will be recalled from the earlier description (1), the examination of each patient calls for a comprehensive and detailed history and a thorough and painstaking physical examination. These partly subjective evidences are supplemented by the objective facts drawn from a somewhat extensive series of standardized laboratory tests and measurements which experience has shown to be significant. The material from both of these sources is essential to a just estimate of the underlying condition. To the basic routine study to which each patient is submitted, a number of special tests and clinical studies are added, these being determined by the needs of the individual patient. They consist of selections from the many well-known laboratory procedures such as special kidney and liver function tests, cardiogram and gastric analysis, and also from the many special examinations carried out by the members of the consulting staff. Each step in the study is taken expectantly as it may either confirm a tentative diagnosis, eliminate a possibility suggested by the results of the earlier study, or, at the worst, indicate other lines of investigation leading to an ultimate resolution of the problem. In the course of the work, certain of these consultations and special tests have demonstrated so general a significance as to lead to their incorporation as a part of the routine. In this latter group, for example, falls the eye examination, including the measurement of visual acuity, examination of the pupils, ophthalmoscopic study, delineation of the blind spots and plotting of form and color fields, the several results of which may throw light on a wide variety of conditions. As will be shown later in the paper, the routine eye examination has established a number of new facts of very real diagnostic significance.

The last phase of the study is concerned with the critical analysis of the collected material and leads to a diagnosis, the authority of which rests on that of the supporting evidences from which it is derived. It is again emphasized that each single test or measurement must be interpreted in the light of all related observations. For example, a low basal metabolic rate in an obese person is interpreted with regrettable frequency as an evidence of thyroid failure. As a matter of fact, it could result from partial protein inanition, with or without a complicating endocrine condition not associated with the thyroid. Obesity is wholly compatible with an inadequate protein intake as the daily fat and carbohydrate content may far exceed the energy requirement of the individual. Inadequate protein will lower the basal rate independently of the remainder of the diet (8).

Further, non-endocrine causes of departures from the normal must be rigorously eliminated by test and observation—not opinion—before the point in question can be given any weight in support of an endocrine diagnosis. The paper already cited (7a, b) offers ample evidence to support this contention.

Finally, it must always be borne in mind that the subjective evidences of the patient's own story are the least dependable of all of the material available. Honest lapses of memory coupled with the suppression of facts and with frank misstatements intended to mislead are all vitiating factors. In a consecutive series of 40 cases of syphilis—from which children with congenital lues were excluded—31 subjects denied a previous infection.

While the subjective data are the least controlled, serious error may also appear indirectly in the laboratory measurements. Failure to collect a full 24-hour urine sample, sophistication of collected material and failure to take all of a provocative test meal, when carried out at home, are all potential sources of misleading figures. Constant vigilance is essential if reliable data are to be secured.

Finally, while the subjective clinical evidences are less reliable than the objective laboratory data, both may be essential to the resolution of the diagnostic problem. One other matter presents itself for careful consideration. The presence of organic or functional disease of an endocrine gland in an individual patient does not preclude the presence of other disease conditions unassociated directly with it. In fact, very many endocrine cases will demonstrate the presence of an intercurrent disease which may equal or even exceed in importance the glandular derangement. As these superimposed conditions all may influence in some measure the various individual data that make up the disease picture, due account must be taken of them.

To render the matter concrete, a group of 500 endocrine cases has been taken from a consecutive series and the relative frequency of the complications which they presented ascertained. These figures have been compared with the 500 non-endocrine cases which were discussed in an earlier paper (7a, b). The result of the study is given in the table.

No definite conclusions can be drawn from the small number of cases in the adrenal and pancreas groups, but the frequent occurrence of tuberculosis and of kidney disease in the adrenal group and of syphilis and cataract in the pancreas group seems significant. In the main, there is a large degree of correlation between the complications and the endocrine disorders. When any given complication occurs much oftener in the endocrine than in the non-endocrine group, it seems logical to assume a causal relationship. In interpreting this table, however, special circumstances in some cases have to be considered. The larger number of mentally retarded patients in the endocrine group rests on the fact that such cases were referred for study only where various stigmata suggested a possible glandular background. Likewise, primary anaemia and ear disease occur with abnormal frequency in the non-endocrine group. We have

TABLE I  
PERCENTILE COMPLICATION OF PRIMARY ENDOCRINE CASES

Complication		Endocrine Group						Non-Endocrine Group (%)
Group	Condition	Pit.	Thy.	Gon.	Adr.	Pan.	Total	
Number of Cases.....		185	160	125	15	15	500	500
Infections.....	Tuberculosis.....	5	8	6	40	0	7.0	5.2
	Atrophic Rhinitis.....	0	1	3	0	0	1.0	0.8
	Arthritis.....	9	7	11	13	13	9.0	4.8
	Tonsils.....	11	11	9	0	13	10.4	
	Sinuses.....	9	10	5	7	7	8.0	5.0
	Other Focal Infections....	9	3	6	0	20	6.6	
Psycho-Neuroses.....	Neuroses.....	8	6	23	0	7	10.8	4.4
	Psycho-Neuroses.....	9	6	13	13	0	9.0	6.6
	Psychoses.....	5	3	2	0	7	3.8	3.2
Nervous System.....	Lesions of Brain and Cord	17	11	2	20	0	10.8	10.0
	Epilepsy.....	3	1	2	0	7	2.2	2.0
	Mental Retard.....	6	4	0	0	0	3.4	1.6
	Physical Retard.....	3	3	0	0	0	2.0	0.0
	Physical Overgrowth.....	1	1	0	7	0	0.8	0.4
	Chorea.....	3	1	0	0	0	1.4	2.6
Metabolism.....	Malnutrition.....	1	0	6	7	7	2.4	6.0
	Obesity.....	25	11	4	0	20	14.6	12.2
	Misc. Bone Diseases.....	2	3	1	7	0	2.2	2.0
Cardio-Vascular System.	Heart.....	8	4	4	0	0	5.2	1.8
	Kidney.....	8	8	13	53	13	10.6	10.6
	Cardiorenal.....	1	4	4	7	7	3.0	8.2
	Hypertension.....	8	7	4	0	7	6.2	6.0
Blood.....	Primary Anaemia.....	0	1	0	0	0	0.2	1.6
	Hemophilia.....	0	0	0	0	7	0.2	0.2
Tumors.....	Malignant.....	1	3	1	7	0	1.6	1.2
	Benign.....	3	1	0	0	7	1.6	2.0
	Non-Toxic Goiter.....	4	0	5	0	0	2.6	1.6
Miscellaneous Conditions	Eye.....	1	3	4	7	29	3.0	2.8
	Ear.....	3	8	4	0	0	4.6	13.0
	Skin.....	5	8	5	0	7	5.6	4.6
	Allergy.....	3	6	5	0	0	4.2	2.4
	Gastro-Intestinal.....	1	7	6	13	0	4.6	3.0
	Liver and Gall Bladder..	10	29	10	0	27	16.4	2.6
	Syphilis.....	5	4	3	0	40	5.2	11.4
	Pelvic Disease*.....	9	2	12	0	0	7.2	3.2
	Menstrual*.....	4	2	4	0	11	3.6	6.0
	Infertility†.....	4	6	8	0	0	5.5	1.2
	Pregnancy*.....	1	1	0	0	0	0.8	1.0
	Uncomplicated.....	5	13	9	0	7	8.4	3.6

\*Based upon females alone.

†Based upon number of patients married.

made a special study of these conditions. The number of non-endocrine syphilitics may probably be traced to the fact that the disease frequently simulated disorders of the ductless glands. The non-endocrine arthritics were reported only when the condition was severe, hence the apparent incidence is misleading. The "uncomplicated" cases in the non-endocrine group were normal controls and thus do not correspond to the endocrine group similarly designated. The patients showing malnutrition were those in whom the diagnosis was based on several manifestations. If reduced weight alone were considered the difference in the endocrine and the non-endocrine groups would be much less.

Turning to those groups where the lack of correlation is seemingly a real one, a few comments may be permitted. The low proportion of focal infections in the non-endocrine group is somewhat misleading since special studies by which they might have been discovered were fewer in number than in the endocrine group. Even making allowance for this fact, however, focal infections occur in the endocrine group definitely more often than in the non-endocrine.

The excess of cases of heart disease in the endocrine group does not depend upon the thyroid factor as might at first be anticipated. It will be noted that the combined cardiac and cardiorenal sub-groups are about equal in the endocrine and the non-endocrine groups. There is no doubt an age element in the distribution, as the non-endocrine subjects were older, and it is possible that the difference here is apparent rather than real.

As will be discussed later, the endocrine group and especially the ovarian patients had had a large amount of abdominal surgery and this may enter as a determining factor in the disproportion of pelvic disease. The unequal number of cases of infertility is not as representative as these figures would seem to indicate, but there is a real difference even without the element of special selection that was operative in this series. The patients with neuroses and liver disorders show real differences, and these will be treated in the body of the paper.

Reverting to the table, the correlations of each complication with the several individual endocrinopathies may be briefly reviewed. Certain of them, such as the high incidence of tuberculosis and renal disease in adrenal failure, could well be predicted. The selective influence of ovarian failure in producing functional derangements of the nervous system is apparent. The association of psychosis with all of the endocrines, but somewhat more with pituitary disease, has been noted in the earlier papers. The raw data are in interesting agreement with the preliminary figures of the far more comprehensive studies of Hoskins and Sleeper (9) recently presented.

The anatomical relationships of the pituitary undoubtedly account for the large number of these patients showing lesions of the central nervous system as complicating factors. The fact that mental retardation appears only in the pituitary and thyroid groups is presumably due to the fact that ovarian failure does not occur at any early age. While the evidence is not yet entirely conclusive, the studies of this institution seem to indicate that the ovary in the human race assumes a real hormonal importance only at puberty. The testicle, on the other hand, has little or no endocrine significance in adult years. The few dependable data obtained from studies of prepubertal castration in man, however, seem to indicate a genuine endocrine function before maturity.

Physical retardation falls in the same category and the sole adrenal case presenting overgrowth was the child (Case C-16) already discussed in an earlier paper (5). The malnutrition of the ovarian case is probably

due to neurotic dietary eccentricities. While neuroses are not confined to ovarian failures, they are most often found in this group. Victims of ovarian failure are notably egocentric. The relative influence of the several endocrine glands in producing obesity is well illustrated. The low incidence of hypertension in the gonad group correlates both with the characteristically low blood pressure of that condition and the freedom from arteriosclerotic changes that often occur in hypothyroidism.

In the cases of non-toxic goiter here recorded the thyroids showed considerable degrees of enlargement. The question of slight thyroid hyperplasia will be considered later. Thyroid patients are seemingly more susceptible to deafness, various forms of skin disease and protein sensitivity. No reason for the low incidence of gastrointestinal disorders in pituitary disease can be offered at present.

The frequent association of gall bladder disease and hepatic dysfunction with thyroid failure has already been noted (3) and finds added support in the present compilation. The relative incidence of severe menstrual disorders in the several groups serves once more to emphasize that these conditions are not essentially due to ovarian failure.

One point requires emphasis. In discussing these data, no attempt has been made to determine specific causal relationships. The data, however, do seem to warrant two conclusions:

1. The occurrence of most non-endocrine complications in the endocrine group and in the non-endocrine group in so nearly equal numbers indicates that significant increase in the presence of a symptom or a positive response to a test in the endocrine group is probably due to the glandular factor.

2. Certain non-endocrine disease states seem to be associated selectively with individual endocrinopathies, although usually represented in them all.

With this general introduction, attention may be directed to the consideration of the pertinent clinical evidences.

*Sex.* That endocrine disorders are reported more often among females than males there can be no doubt. The figures of this institution show a ratio of three females to one male, and that this is not due solely to psychological factors is attested by the fact that in our parallel non-endocrine group the ratio is three to two. Only the diabetics show an exception, the female incidence here being slightly less than in the non-endocrine group. Significant departure from the group average is shown by the pituitary which approaches the non-endocrine frequency (63 per cent) and by the gonad group which is composed almost exclusively of women (96 per cent). The apparently extreme rarity of functional or organic change in the testicle of sufficient magnitude to require medical aid has been discussed elsewhere (4).

*Age.* About 60 per cent of the pituitary cases come to investigation before they are thirty; the thyroid scatter is fairly uniform throughout the first six decades; the ovarian diseases seemingly do not begin until

after the establishment of the catamenia, but nearly 40 per cent are reported during the third decade; adrenal disease is chiefly an incident of the years from 20 to 50. In general, as shown in our series by comparison of 1250 endocrine with 1000 non-endocrine cases, endocrinopathies have a somewhat earlier onset than other diseases.

*Age of Onset and Duration.* The reports on this event are unduly colored by the subjective character of the basic datum, most strikingly illustrated in the patients who report the chief complaint as dating from birth. A further cause of error lies in the very human tendency to ascribe the cause to some striking event in the life history which in many cases is wholly unassociated with the true condition. Including the congenitally defective and those claiming onset at birth, in 38 per cent of the pituitary cases the beginning of the chief complaint is dated before the eleventh birthday, while but 20 per cent of the thyroid and 10 per cent of the gonad disorders fall in this decade; the non-endocrine record shows 14 per cent. Sixty-four per cent of the gonad disorders are reported as beginning in the second and third decades; all of the remaining percentile values show an approximate uniformity, the major differences being compensated before the thirty-first birthday. The concentration of the gonad cases in the latter half of the second and the whole of the third decade, normally the period of largest fertility, is possibly suggestive.

As the duration of the disorder is calculated from the alleged date of onset, it is equally subjective. For what value may be in them, it may be recorded that assuming conventionally for intervals (a) less than one year, (b) from one to five, (c) five to ten, and (d) over ten years, the endocrine distribution is practically uniform throughout. The non-endocrine group concentrates in the second period (43 per cent) at the expense of the first (13 per cent).

*Chief Complaint.* The patient's presentation of the case hinges directly on the chief complaint or, in the great majority of instances, complaints. From its subjective character, this may be the least important piece of evidence in the entire study, depending as it does on a variety of mental factors as well as physical elements. The neurasthenic with a long circumstantial tale in which real and fancied disabilities are hopelessly interwoven stands at one extreme while the emulator of the Spartan youth imbued with a morbid fear of self-revelment defines the other. Ladies over 100 per cent above their predicted weight scorn to list obesity among their disabilities, while others, fully 20 per cent below their predicted normal, offer overweight as the reason for their reference to the clinic.

With the dominance of the subjective element, a wide scatter is to be anticipated in the symptoms as offered. Certain of them, however, recur with a frequency that both breeds confidence in their existence and also lends to them a possible diagnostic significance.

With a just recognition of all of these factors, and in the interest of economy of space, discussion will be limited to those individual points

which show differences of diagnostic significance. More complete and detailed analysis must be reserved for later presentation. The omission of a large number of symptomatic data does not mean that they have been ignored in the analysis but that their inclusion would be confusing. This applies particularly to the many non-endocrine conditions discussion of which must be limited to basically significant differences.

*Fatigue.* Reports of asthenia and of a fatigability wholly disproportionate to previous physical exertion is a common complaint in all of the endocrine disorders. Least in evidence in pituitary disease (48 per cent) and most in adrenal disorders (93 per cent), it definitely suggests an endocrinopathy. Non-endocrine states with very high incidence of fatigue are tuberculosis, cancer, and primary anaemia.

While no attempt should be made to delimit the picture too sharply, the fatigue story of the several endocrine entities shows certain possibly suggestive differences. In pituitary disorders, a loss of endurance is a marked feature. There is no asthenic crisis as with the adrenal, but the day's productivity becomes less and the effort greater to produce even a meager return. The thyroid patient awakes unrefreshed, but as the day progresses there is an improvement. At some time, varying greatly among individuals, an apex of well-being is reached which, while never high, contrasts favorably with the condition on awakening. The peak, however, is soon passed and the patient rapidly declines to a level of real exhaustion which persists. In ovarian disease the patient is just "tired all the time," a subjective element being especially noticeable. Finally, the adrenal case in the earlier stages shows an intermittency; brief periods of well-being are rapidly followed by periods of real exhaustion from which the patient recuperates only to repeat the cycle. As the condition progresses, the asthenic intervals become longer and finally determine the terminal condition.

*Tremors.* While the condition is pathognomic in hyperthyroidism and of frequent report in the dysfunctional states of this gland, all of the endocrine group, particularly the ovarian failures, show a fairly high incidence. Asthenia and nervous instability, from whatever cause, are factors in its production.

*Nervousness.* This is one of the most subjective of all reported symptoms. It is an omnibus term, including a number of aspects of nervous instability and not infrequently is offered as an excuse for selfishness, undue irritability, and kindred personality defects. A by-product of numerous non-endocrine disorders, it is dominantly present in all of the endocrine, least apparently in the pituitary cases, and an invariable feature of ovarian failure. The psychoneurotic group and that of the central nerve lesions account for the main portion of the non-endocrine cases, but syphilis and cardiovascular disease each make an appreciable contribution to the total.



*Paraesthesias.* Numbness, formication, and cramps are frequently reported by thyroid and adrenal patients, less often in the other endocrine states. As symptoms, they occur with like or even greater frequency in a number of non-endocrine conditions.

*Pain.* In the endocrine group pain is frequently not localized with any marked specificity but is rather a generalized condition. Of frequent report in hyperpituitarism and Addison's disease, the highest incidence is found in the group of ovarian failures. In fact, any symptom associated with a pain impulse is usually found most frequently in this group. Thus, headache is common among the hypogonad patients, exceeding in frequency the report of the pituitary group, in which there may be a material cause for the symptom.

*Obesity.* All of the major endocrine groups show a high incidence of this symptom, although its report as a complaint lags far behind its actual frequency of occurrence. The pituitary leads with nearly 50 per cent, while one in three of the thyroid subjects and one in four of the ovarian failures are at least 15 per cent overweight. The selective girdle distribution of the pituitary may merge to a suggestion of the generalized thyroid type in patients who are more than 100 per cent above prediction.

In ovarian failure a fat body with thin legs is common. Localized evidences such as the supraclavicular pads of thyroid failure are easily obscured in the truly obese. Critical analysis demonstrates the unwisdom of basing a diagnosis on fat distribution. A large number of non-endocrine states are associated with overweight, not the least significant of which is simple gluttony.

*Underweight.* While rarely figuring as a chief complaint, it is of relatively frequent occurrence. Many hyperthyroid cases show underweight and as many thyroid failures were below as were above prediction. Early in these studies a type of thyroid failure was recognized on objective grounds which departed notably from the conventional picture of hypothyroidism. These patients were thin; mentally and, in some measure, physically, alert; not sluggish; did not exhibit myxedema and offered yet other significant departures from convention. They presented, however, typical laboratory pictures (including basal rates below—30 per cent) and showed a normalizing of the clinical and laboratory picture, including gain in weight, under the stimulus of thyroid therapy. The condition has been described elsewhere (3, 10). Rapid upward changes in weight are suggestive of a modified endocrine status, while the opposite condition suggests equally wasting non-endocrine disease or an endocrinopathy.

*Overgrowth.* This does not include early sexual maturity and usually implies a pituitary disorder. An influence of the testicle in prepubertal years has been recorded by others. Unfortunately there are no cases in this series in which a testicular involvement could with certainty be dated prior to maturity. In this particular field, in which unbridled speculation has played so dominant a rôle, it seems best in this summary to adhere to observed facts.

*Undergrowth.* Both thyroid and pituitary disease are associated with this state as, equally, are injuries to the central nervous system and syphilis. As might be anticipated, the ovary seems to play no part in producing this condition.

*Mental Retardation.* Again, only the pituitary and thyroid seem to be involved. An interesting fact is that but half of the children referred to as feeble-minded are found to be so on careful psychometric study.

*Disorders of the Eye.* The results of actual measurement will be considered later. Pain, blurring of vision, and spots before the eyes are frequently reported in the ovarian cases. The association of cataracts with diabetes is well known. Poor vision is a uniform report, the pituitary showing no superior influence traceable to its anatomical relationships. Fatigue is also a common and characteristic symptom.

*Disorders of the Ear.* Tinnitus is a common endocrine complaint most often reported in the ovarian cases, as also is a record of pain.

*Disorders of the Nose.* The entire endocrine group is seemingly susceptible to colds and to catarrh. Over 50 per cent report one or the other or both. Both the pituitary and gonad groups report epistaxis with significant frequency.

*Teeth.* While one in ten of endocrine and non-endocrine subjects alike have had all the teeth removed, a poor condition of these important structures is much commoner in the endocrine group. The ovarian cases lead, the thyroid group comes next, while those with pituitary disease are but slightly superior in relative numbers to the non-endocrine group.

*Goiter.* Inasmuch as a thyroid enlargement is frequently the sole basis of a diagnosis, it is interesting to note that while 11 per cent of the thyroid subjects complained of this condition, 3 per cent each of the pituitary and ovarian patients made a similar report (See "physical examination" later).

*Disorders of the Cardiorespiratory System.* Dyspnoea without palpitation is a strikingly frequent secondary report in ovarian failure, as is pain in the chest. One in eight of the thyroid patients reported either dyspnoea, palpitation, pain, or cough as a chief complaint, while the pituitary and gonad figures are respectively 0 and 5 per cent. Cough is significant as a report only in hyperthyroidism.

*Disorders of the Gastrointestinal System.* As a chief complaint, conditions associated with the alimentary tract are encountered in all of the endocrinopathies, the pancreas and adrenal leading. Nausea and vomiting are frequently recorded in all; the ovarian group leads in the report of pain, the adrenal in flatulency.

The reports of jaundice are really interesting. As an earlier incident, it was reported by a smaller group of pituitary subjects than were actually demonstrated to have disorders of the liver and gall bladder. This was repeated much more strikingly in the thyroid group where the relative percentages were 10 and 29 respectively. It is certain that a portion of the hypogonad subjects interpreted sallowness of the complexion (and

possibly earlier chlorosis) as jaundice, although the group as a whole showed a 10 per cent incidence of demonstrated hepatic dysfunction (See Table I). Two of the pigmented adrenal patients reported their skin condition as jaundice and, on the other hand, the two diabetics reporting this condition were but half of the number presenting the "bronzed" type of the disease.

Constipation is a usual, diarrhoea a rare report. In the former condition the thyroid and gonad groups show the highest incidence. It is to be remembered that the term is a relative one. Adrenal patients have genuinely poor appetites.

*Disorders of the Genito-Urinary System.* The concomitant involvement of the kidneys in adrenal disease is the outstanding feature. Nocturia is common to all, dysuria characterizes the ovarian patients.

*Disorders of Menstruation.* This topic will be discussed more fully later. They were a chief complaint in 15 per cent of the ovarian cases and 10 per cent of the pituitary. Nearly half of the former complained only of dysmenorrhoea, this fact influencing in a misleading manner the figures for the chief complaint.

*Abnormal Temperature Sensations.* The adrenal, gonad, and thyroid patients complained of cold in the order named. If "hot flashes" be eliminated, the opposite condition was rarely mentioned.

To summarize the foregoing briefly, the following may be stated:

In the main, the patient's complaints fail to indicate any real endocrine influence. Definite exceptions are found in reports of fatigability, disorders of dentition, dyspnoea alone and pain in ovarian failure, susceptibility to infections of the upper respiratory tract, mental retardation in pituitary and thyroid disease, overgrowth in pituitary disease, and the general observation of obesity with possibly a significantly selective distribution. Less certainly or significantly should be named "nervousness," nocturia, hypothermia, together with canker, skin diseases, and cough associated with the several types of thyroid disease. Further, no one of these conditions can be regarded as more than suggestive, very appreciable representation of each of them being found in the non-glandular group. In other words, the positive yield is small and concerns itself with trends, not definitions. On the negative side, however, the case is much more hopeful as every symptom points the way for further investigation, the concrete return of which may be the definite inclusion or exclusion of really significant factors. The suggestive quality of this type of evidence cannot be overestimated; it is vital to an adequate consideration of every case. But its straightly defined limitations should ever be borne in mind and give pause to an enthusiasm that would erect a final diagnosis on so uncertain a foundation.

*Family History.* Cancer and tuberculosis are very generally reported in both major groups. Diabetes is found in 9 per cent of the endocrine and 7 per cent of the non-endocrine group, while the similar figures for familial thyroid disease are 7 per cent and 3 per cent. Recognizing that

pituitary disorders have been less frequently recognized in the past from their usual lack of easily recognized stigmata (acromegaly being of course an exception), the figures for a familial endocrine influence certainly fall short of the truth. Even so, the data obtainable are striking and evidence a real influence in the establishment of what may be termed a constitutional endocrinopathic tendency which is not specific to the gland involved.

A family history of endocrine disease is obtained in pituitary disorders, 21 per cent; thyroid, 14 per cent; ovary, 17 per cent; adrenal, 13 per cent; pancreas, 33 per cent; non-endocrine group, 10 per cent.

Obesity is reported as a family trait seven times as frequently in the endocrine as in the non-endocrine group. It, like non-toxic goiter, however, is greatly influenced by outside considerations; the large disproportion is none the less suggestive.

*Past History.* In largest measure, these data realize their true significance only in providing a background in the individual case. For example, castration determines an unmistakable endocrinopathy in the individual subjected to it, but the fact is without meaning in indicating any trend of import for differential diagnosis. Earlier encephalitis influences the individual greatly but does not bear on the general problem. Rarely does analysis yield figures which warrant interpretation in terms of general or specific endocrine cause or effect. The following discussion will be limited to the few observations which are seemingly pertinent.

(a) *Previous Diseases.* A history of earlier tuberculosis is found with unique frequency in the group of adrenal cases.

Tonsil and sinus infections appear with much greater frequency in the endocrine group; the distribution is general.

The report of earlier venereal disease is significant only as it emphasizes the unreliability of personal report on this point.

The remaining conditions, nineteen in number, show a general scatter that is devoid of significant trend.

(b) *Surgical History.* Nearly half of the endocrine subjects had had one or more tonsillectomies, a much higher proportion than in non-endocrine cases. The same disparity was evident in sinus operations, though the total number was much smaller.

The ovarian subjects showed a much larger percentage of appendectomies than any other group; in fact, they nearly equaled the sum of the thyroid and pituitary patients reporting it. Further, they reported nearly three times as many repair and suspension operations and hysterectomy had been performed in 8 per cent as against 2 per cent in the thyroid and 1 per cent in the pituitary groups. Seven per cent had had one ovary removed, the total relative incidence in the other two major endocrine groups together. Finally, 15 per cent had been castrated, this last, of course, being a record confined to this group alone.

The association of ovarian failure with abdominal section is worthy of brief further consideration. Omitting complete castration and dilata-

tion and curettage (in which hypo-ovarions show a marked superiority in numbers), the following relationship obtains:

TABLE II

Percentage of women showing at least one operation requiring abdominal section.

Pituitary .....	17%
Thyroid .....	14%
Ovary .....	42%

The patent association here is frankly susceptible of two interpretations. The first, namely, that ovarian failure predisposed to the development of disease in the abdominal and pelvic organs would have a far firmer foundation if the operations recorded were confined to the internal genital apparatus. This is, however, far from being the case. On the other hand, it seems a supportable thesis that the manipulation incident to the various operative procedures, possibly through indirection, may lower the functional levels of these important glands. The question cannot be settled here, but waiving factors of causation, it seems fair to say that a history of abdominal interference offers a suggestion of possible ovarian failure.

(c) *Traumatic History.* The pituitary cases definitely exceed the other major endocrine groups in the report of head injuries and equal the non-endocrine group which contains a number of patients with traumatic injuries of the central nervous system.

*History of the Catamenia.* This will be only briefly touched on as the topic is to be treated in detail elsewhere. An analysis of some nine hundred endocrine cases shows nearly 10 per cent maturing before the 12th birthday. Only the ovarian group shows significantly lower figures (5.5 per cent). Nearly 20 per cent show a delayed onset, with the function not established before the 15th birthday. Recognizing that these limits are conventional, they none the less serve to establish relative values. Incidentally, the figures in the non-endocrine group are substantially the same, a fact which urges conservatism in the interpretation of an abnormal menstrual history.

Further considerations deal with the interval of the rhythm and with the duration and amount of the flow. Waiving the niceties of a detailed statistical analysis, the following conclusions may be noted, recognizing that they define tendencies only:

Endocrine disease in general is associated with a larger percentage of menstrual irregularity than is found in an equivalent non-endocrine group.

Pituitary disorders tend to produce a prolonged interval with normal or progressively scanty flow.

Thyroid disease is associated with a true irregularity, the interval being both longer and shorter in the same individual and the flow at times

scanty, at others profuse. This latter is far more characteristic of thyroid disease than of any of the other endocrine states.

Failure of the ovaries follows the general course of the pituitary cases, but the scanty periods manifest themselves earlier after the interval has begun to lengthen.

The adrenal cases differ only in degree from the pituitary, with increasing interval and usually normal flow.

Many non-endocrine conditions produce similar pictures but with definitely lessened frequency of appearance.

The one basic fact to be learned from this consideration is that menstrual irregularity does not inevitably imply a primary ovarian failure. Actually about 40 per cent of the hypogonads are entirely normal and another 40 per cent abnormal only in interval or amount.

*Marital History.* This topic also will be touched upon very briefly as extensive studies are shortly to be reported. About 50 per cent of all of the groups under consideration had been married one or more times. A single exception was the adrenal group with but 29 per cent. Fertility data are not highly significant as the study of the single patient deals with but one partner. As presumably, however, the same factors operate in each group, the relative data have a modest significance.

The endocrine patients were definitely less fertile than those with non-endocrine disease even though the latter group contained an appreciable number of syphilitics and patients with other conditions recognized as influencing fertility. The pituitary shows the same relative number of conceptions per marriage as does the non-endocrine group; the other endocrinopathies a lower value, the thyroid, gonad, and adrenal following in the order named. All of the adrenal pregnancies were successful (the small number involved robs this fact of real statistical significance) and three in four of both the pituitary and thyroid pregnancies terminated in viable children. Only two in three impregnations of the ovarian subjects yielded living issue, there being a high incidence of miscarriage. As their percentage of reported abortions was also the highest, it may well be that the large total of miscarriages was more apparent than real. Whatever the agency, nearly half of the ovarian cases were unproductive, about one-third of both the pituitary and thyroid groups, and only one-fourth of the non-endocrine series.

It seems warrantable to conclude that endocrine disease constitutes one hindrance to a fertile union and that ovarian disease seems to exercise a larger measure of influence than do the other members of the group. The second is tentative and possibly subject to revision; the first is established.

#### PHYSICAL EXAMINATION

While the data under this caption are far more objective in character, there yet remains a subjective element for which due allowance must be made in interpretation.

*Development and Nutrition.* The actual development of the individual as reported here is in largest measure a matter resting on the judgment of the examiner and inevitably influenced by the state of the patient's nutrition. Gross developmental defects are patent, but in the inspection of the average non-deformed individual the criteria for designation will show a fairly wide range. If the usual assumption be made that these adverse factors will operate uniformly in groups of sufficient size to absorb individual variation, the figures assume a certain significance. The endocrine group records a slightly larger incidence of individuals showing good development than does the non-endocrine, the pituitary leading by an appreciable margin. This record is remarkable as the endocrine glands are conceded to be potent regulators of growth and development. It must be remembered, however, that the large majority of the endocrine cases studied were in adult years and the onset of the prevailing difficulty had very frequently postdated the growth period. With this consideration the apparent contradiction disappears and the conclusion to be drawn from the developmental report is that it has no selective significance in any general sense. Naturally, reservation is made in favor of the dwarf or the giant, but this condition affects the individual, not the group. The achondroplasias of these series were all without evidence of any endocrine disorder and showed a relatively high incidence of luetic taint.

The nutritional values reflect the early reports on weight. The pituitary shows the most pronounced tendency toward overweight, the adrenal the least. The thyroid partition is striking in that the three percentile values for normal, overweight, and underweight are 34, 33, 33, a fact that is somewhat far reaching in its significance.

The thyroid cases show a higher association with eczema, psoriasis, and keloid, the gonad patients with acne. There is no real differential significance as all of the groups show an incidence of some kind of skin eruption equal to one in four.

While only the adrenal patients showed frequent pigmentation, a few hyperthyroid subjects exhibited skin changes characteristic of this condition. Four of the diabetics were of the bronzed type; they were all referred as potential cases of Addison's disease.

Marked varicosities, chiefly in the lower extremities, are frequently observed in pituitary disease. Slight varicose enlargement is a fairly general finding throughout the entire endocrine group.

The amount and distribution of the hair in various parts of the body requires the exercise of great caution in its interpretation. Such factors as race, employment, and similar wholly extraneous agencies may profoundly affect either standards or occurrence.

Broadly speaking, thyroid failure tends to produce loss of hair from the vertex in individuals whose age does not make the occurrence a natural one. The interpretation of abnormal arrangement of the eyebrows

in terms of thyroid failure has notably less to recommend it as a sound diagnostic procedure.

Hair on the face usually follows the course of that on the body, although females with facial hypertrichosis and normal body hair are not uncommon. General hypertrichosis and particularly a male distribution of pubic hair is most certainly associated with pituitary disease and with ovarian failure. Its attribution primarily to tumors of the adrenal cortex is not warrantable (4), although they are seemingly also a factor. Scanty body and facial hair is associated both with pituitary and thyroid conditions, more marked in the former and chiefly in cases of an underactivity beginning in the earlier years of growth and development. Loss of body hair in the adult, in the writer's experience, is more frequently met in pituitary than in thyroid disorders, although observed in both. In relation to the pubic hair alone, with its normal differentiation dependent on sex, it may be briefly stated that male distribution of pubic hair in the female suggests ovarian or pituitary disease, scanty normal distribution, pituitary or thyroid. Notably heavy normal distribution in the male suggests pituitary, female distribution the same gland or possibly the thyroid, while a scanty adornment of the pubes is found in both pituitary and thyroid disease. In addition, heavy pubic hair growth may be associated with disease of the adrenal cortex.

*Eyes.* With the exception of the mechanical effect of pituitary tumor, exophthalmos in hyperthyroidism (to which it is not exclusively confined) and cataract in diabetes, no specific and characteristic eye effects, demonstrable by routine examination, are traceable to endocrine influence.

*Nose.* Deviated septa, nasal discharges, and tender sinuses are frequently found throughout the endocrine series.

*Teeth.* Examination of the dentition serves to confirm the reports in the history. Actually the incidence of poor teeth is higher than the report in all the endocrine groups save that of the highly subjective ovarian failures; an endocrine association with poor dentition is apparent.

*Tongue.* Tremor of the tongue is not confined to the thyroid patients, although exhibited somewhat more frequently by them. The ovarian cases also show a relatively high frequency.

*Tonsils.* The earlier records showed an apparent endocrine association with tonsil infection, both in the reports of previous tonsillitis and of tonsil operations. Physical examination confirms and augments the earlier record, nearly twice as many endocrine as non-endocrine cases showing definite infection. This is the more striking as many more of the endocrine patients have had tonsillectomies. The recognition of infected tonsillar remnants should operate about equally in both major groups. An association is certainly proven; if it be causal or resultant remains to be resolved.

*Thyroid Enlargement.* The present findings were in some measure foreshadowed in the earlier comment on goiter. Actually, thyroid enlarge-



ment was observed as follows: Pituitary 18 per cent, thyroid 34 per cent, ovary 25 per cent, non-endocrine group 10 per cent. While the thyroid naturally leads, the occurrence is too frequent in the other endocrine groups for the observation to assume marked diagnostic meaning. Further, two-thirds of the proven thyroid cases did not show significant hyperplasia.

*Breasts.* Growth abnormalities of the breasts show a significant frequency only in pituitary disease, though under-development is associated fairly often with ovarian failure. The fat breast of the very obese male does not enter into this consideration as it is only one expression of the obesity.

*Heart.* Murmurs are significantly frequent in both pituitary and thyroid disease, while the ovarian cases show an even more striking absence of this sign.

Tachycardia characterizes the overactive and dysfunctional thyroid cases and in lesser degree, though not in frequency, the ovarian failures. Significant bradycardia is chiefly found in the hypothyroid group.

*Abdomen.* A generalized tenderness is characteristic of the hyper-sensitive ovarian failure. Its report in the obese is sometimes due to a well-meant enthusiasm in overcoming anatomical obstacles.

*Male Genitalia.* One in three of both the thyroid and pituitary groups show abnormalities such as general atrophy or hypertrophy, and undescended or atrophic testicles. The large incidence in the small male gonad group is to be anticipated, and in every positive case not a castrate was a post-orchitic atrophy following mumps. The overgrowth of the external genitalia in pituitary disease is the only feature of apparent single association.

*Spine.* Lordosis appears with significant frequency in the pituitary and thyroid groups and the few cases with kyphosis only in the former. Tenderness along the spine is reported in significant measure only in the gonad cases and is seemingly but one more instance of the dominance of a pain element in their picture.

*Neuro-Muscular System.* In the main, the weight of the significance of abnormality in this field lies in the suggestion of complication rather than of specific endocrine effect. Increased and diminished knee jerks are found in all groups and the percentile representation denies any specific influence of an individual gland.

*Mental States.* There were fewer cases of real mental retardation and more of psychosis in the endocrine than in the non-endocrine group. In the latter category the gonad and pituitary groups show a slight preponderance but not sufficiently to have differential significance. The field here is a new one to objective study and is of vital importance. It will form the topic of a later publication.

*Personality.* The prepubertal pituitary case is frequently that of a child with a behavior problem. Real mental retardation is found with

certainty only in the Frölich syndrome; with many of the others, wandering attention is the real cause of the report. Many of these patients normalize spontaneously during the physiological readjustments of adolescence. In the really defective cases the glandular state may be no more than secondary to injury to the central nervous system. This is peculiarly true in patients with increased intracranial pressure.

In adult years, the pituitary cases, unless carrying an initial handicap as suggested above, include a large percentage of normal people and not a few whose intelligence is distinctly superior to the average. A small number show apathy, indifference, a heavy ill-nature, and mental sluggishness; they are less characteristic than those previously described.

While the cretin is the prototype of congenital thyroid failure, many children are found with hypoactive thyroids who depart definitely from the classic picture. They are mentally retarded or, at best, sluggish and are ill-natured with a heavy sort of negativism. They are incooperative and frequently asocial.

The personality in the adult thyroid case reflects in some degree the functional level of the gland. In the hyperactive and transition cases the subjects are tensely nervous and usually exhibit a marked degree of instability which translates itself into an easy irritability, fearfulness, and apprehension. Thyroid failure also results in a nervous instability which, however, finds expression in other terms. The subjects are self-centered, negativistic, and truculent, but the condition of ill-nature is of the type of a deep heavy anger rather than a sharp outburst. They resent the necessity of cooperation but manifest the reaction in a negative rather than positive form; they are sullen rather than aggressive.

Mental sluggishness is a fairly common feature of failure with myxedema and a normal mentality in the amyxedemic type is generally seen. The other function levels offer nothing distinctive.

In ovarian failure the subjects are insistently egocentric and that in a shrill and voluble fashion. They are highly incooperative and selfish but in a positive manner, the antithesis of the thyroid type. Their condition affords fertile soil for the growth of the major forms of hysteria.

The male castrate exhibits a profound mental depression but is otherwise normal. Even this inhibition has been known to be dissipated by the demonstration of a partial masculinity [see (4), Case B-42].

The social reaction in adrenal failure is conditioned by the very real asthenia that characterizes the disease.

## SECTION II

### *Laboratory Measurements*

The body of this portion of the paper will be devoted to a discussion of certain of the objective findings obtained by direct measurement or laboratory procedure. These form the group of objective facts on which the method of diagnosis is based. As previously stated, they are not compe-

tent in themselves to determine the diagnosis, but in addition to their important specific significance they offer fundamental criteria for the true evaluation of the more subjective portions of the study.

In the discussion of the clinical evidences it was usually possible to consider each endocrine gland as an entity, and only occasionally did the permutational influence of different function levels enter into consideration. With the present series of facts, on the other hand, amounts as well as directions are important, and many of the more valuable differential data derive their ultimate significance from the quantitative relation. On this basis the presentation of trends is both more significant and practical than that of actual averages, since the inclusion of incipient and early cases in a general series dilutes the differential values so strikingly exhibited in the established individual case.\*

For purposes of definition "hypofunction" is used for that condition most certainly produced by surgical ablation of the gland, or with practically equal authority when it can ultimately be shown to have been destroyed by disease. Presumptively the like designation is correct in those functional states where the disease picture is identical in kind with that of demonstrated insufficiency.

"Hyperfunction" designates a condition in which all of the factual evidences are directly opposite to those characterizing the known hypofunctional state.

"Dysfunction" is that condition in which individual findings are found simultaneously which are associated with both augmented and depressed functional levels in the given gland. These may arise in transition states of functional involution or from different function levels in the several structures of the composite glands.

To save space and render the data more concrete, the significant facts may be presented in tabular form. Further, since trends are to be considered, simple symbols may be used which require a word of explanation.

For those measurements where the qualitative appearance of abnormal findings is the significant datum, the symbols  $+$  and  $0$  will be used in their usual connotation. The significance of the majority of the data, however, depends upon the direction and amount of departure from the level observed in health. It may be said that *all changes reported here are based upon comparison with the results of an elaborate series of control studies conducted with groups of demonstrated healthy individuals.*

The symbol  $>$  is used to designate increase, the magnitude of the tendency finding expression in the number of symbols used. The opposite symbol  $<$  indicates decrease, and uses the same conventions. The letter N indicates normal performance. When the tendency is variable the first symbol indicates the usual trend, the second a less frequent but still significant alternative.

\*In the subsequent discussion it will be understood that the statements refer only to experience in the human race. The delimitation of study to this group imposes certain obvious restrictions which, however, are more than compensated by the direct applicability of the results obtained.

In the tabulation only the hypofunctional states will be usually considered. Only the thyroid and pituitary, of the five glands under consideration, exhibit other function levels with certainty and significant facts associated with these latter will be treated in the text. Where mention is omitted it may be assumed that the findings for the higher function levels repeat those observed in failure.

TABLE III  
PHYSICAL MEASUREMENTS  
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Weight.....	>>>*	>> or <	N or >	N or >	<<
Lung Volume.....	N or <	< or <<	N or <	N	<<<
Temperature.....	N	<	N	N	N or <
Pulse.....	N or < sl.	< or <<	N or >	N or < sl.	N or sl. >
Respiration.....	N	< or N	N or >	N	N or >
Blood Pressure...Sys....	< sl.	< or <<	< or <<	< sl.	<< or <<<
Dias....	< sl.	< or <<†	< or <<	< sl.	<< or <<<
Alveolar CO <sub>2</sub> .....	N	N	<<	N	<

\*The Lorain-Levy type is a significant exception.

†See text.

*Weight.* Pituitary failure not only conduces to obesity but the tendency is more pronounced and the degree of overweight relatively greater than with the other glands.

Thyroid failure shows a similar but less marked tendency both in degree and kind. The subject of the associated type without myxedema is usually underweight and gains flesh under the normalizing influence of thyroid therapy.

Ovarian failure is more frequently associated with normal weight but a tendency to obesity is unmistakable though less pronounced. The male castrated in adult years shows a tendency to maintain a normal weight. Less frequently obesity of moderate degree is observed. If the basis of the mutilating operation were a wasting disease, as is frequently the case, some degree of underweight may persist for many years after the event. The fat eunuch is seemingly the product of a prepubertal emasculation.

The adrenal subjects, from the character of the underlying etiology of their condition, show a definite tendency toward emaciation. Obesity does not preclude the existence of Addison's disease but usually indicates an early stage of the condition [See (5) Case B-977].

Pituitary dysfunction determines a tendency to obesity only less marked than that of bilobar failure. The appearance of the condition in the hyperfunctional cases may be an evidence of beginning functional involution as the usual habit is a normal weight.

The thyroid shows a wide swing in weight extremes as the patient with hyperfunction shows an emaciation that is one expression of the in-

creased metabolism. The dysfunctional patients are usually of normal weight, but may exhibit either some measure of emaciation as a residuum of earlier hyperfunction or an incipient obesity which foreshadows the approach of established glandular failure.

*Lung Volume.* This quantity, often picturesquely called the vital capacity, is readily determined with the spirometer, and has demonstrated a real significance.

Pituitary failure, even when coupled with a marked obesity, usually produces but minor downward changes in the quantity, and not a few subjects give readings even superior to the somewhat exacting normal standard. Hypofunction of the thyroid, on the other hand, uniformly lowers the observed value below that of prediction and in many cases far below that to be inferred from the general physical impairment. Ovarian failure follows the usual trend of the pituitary in sense and amount; the male gonad case is normal. Marked depression is noted in those adrenal cases in which the characteristic asthenia is well established, as in Addison's disease. It is much less marked in the group conventionally designated as "hypoadrenalism."

The test is peculiarly susceptible to subjective influences, and a lack of hearty cooperation may give values far below the truth. Hyperactive thyroid subjects perform as do the established failures; the dysfunctional group approach a normal level of performance.

*Temperature.* The body temperature is important both for suggestion of intercurrent disease, and for its direct influence on the basal rate interpretation. With the exception of the thyroid in marked degree, and the adrenal in much lesser measure, no specific endocrine influence is apparent. With thyroid failure there is a depression of the temperature of no uncertain proportions. Values below 97° and, rarely, below 96° have been recorded. The hypothyroid "feels the cold" and frequently the body temperature offers a partial explanation. This thermal effect apparently disappears in the other functional levels of the gland. While there may be a slight upward tendency in hyperfunction, it is far from marked and many of the patients are entirely normal in this respect.

*Pulse.* The pituitary failure shows a slight downward tendency which is rarely marked and frequently absent. This latter is not due to a nervous response, as measurements repeated daily over appreciable intervals and under non-disturbing conditions attest. The pulse of the thyroid failure is always slow, and in extreme cases values below 40 are not unknown. Where the functional condition is well established outside disturbing agents have but slight effect on the rhythm; in patients merging from an earlier dysfunction, excitement may produce a tachycardia which is transitory, as demonstrated by repeated observations. The ovarian cases give normal or somewhat increased pulse rates. The nervous instability so characteristic of these patients is certainly a factor in the latter. There seems to be, however, a true if slight accelerating impulse in the condition. Removal

of the testicles, where any influence can be recognized, seems to exercise a slight slowing effect but it is never marked. The adrenal pulse is normal or slightly accelerated. A nervous element associated with the asthenia may exercise a causal influence.

At the other functional levels, the pituitary shows no more influence in dysfunction than in failure; in fact, a normal pulse is the prevailing observation. With the hyperactive gland, however, there is usually a slight acceleration and the prevailing rate somewhat exceeds the normal. With the thyroid, on the other hand, notable changes are produced. Tachycardia is one of the most characteristic observations in patients with overactive glands, and very high rates are frequently recorded. The influence of the thyroid on the heart beat is unique among the endocrine glands, at least so far as degree is concerned. The dysfunctional thyroid may show rapid or slow pulse, depending largely on the degree of involution. The rapid pulse is the more frequent observation—in fact, in glands undergoing downward change a residual rapid pulse may be associated with a really significant depression of the basal rate. In the recessions characteristic of transition, the initially rapid pulse seems to lag behind all other evidences in reaching the terminal phase of established hypofunction. This point is of importance in the interpretation of otherwise contradictory data.

*Blood Pressure.* The actual levels of this important datum, especially the systolic pressure, are peculiarly at the mercy of extraneous nervous impulses. Dependable records, secured where necessary by frequent repetition, show the following relations.

Pituitary failure determines a slight drop in both the systolic and diastolic pressures which in the majority of cases is tendential rather than defined. The thyroid failure shows a depression always of concrete magnitude, and in many instances falls below 100 mm. for the systolic level. A definite exception is shown in the case of patients with long-standing myxedema where the arteriosclerotic changes characterizing the progress of this condition may raise the initially low blood pressures to normal or even hypertensive levels. The ovarian failure habitually records blood pressure levels on a parity with those of pronounced thyroid failure. With basal rates but moderately depressed, and normal or accelerated pulse rate, there is in this fact a definite differential significance. Removal of the testicles seems to produce a slight lowering in blood pressure, one of the very few objective results seemingly associated with the condition, but possibly an aftermath of the initial disease condition.

The hypotensive levels of adrenal failure are characteristic, and in conditions of like severity far more pronounced than those resulting from any other endocrine failure. Pituitary dysfunction repeats the levels observed in failure, but in hyperfunction a tendency toward hypertension has been recorded. The complication of many of these with demonstrated renal involvement raises a question that can not now be answered. Thyroid dysfunction shows a normal systolic and low diastolic pressure producing

a pulse pressure above the normal. In hyperfunctional states this becomes even more marked as the systolic pressure tends toward hypertensive levels, while the diastolic remains normal or below. This large pulse pressure is seemingly characteristic—at least, no other endocrine condition exhibits it systematically.

*Alveolar Carbon Dioxide.* This is another measurement dependent on cooperation. Thyroid levels are slightly below those of pituitary failure but both are normal. The male gonad shows no influence, and there is a slight downward tendency in adrenal disease, possibly traceable to a mild retention acidosis. Ovarian hypofunction frequently produces a drop of significant proportions suggestive of a mild acidosis of which, however, any other evidence is lacking. The same condition is found in pregnancy. Hyperthyroid patients may exhibit a slight depression, possibly a minor result of a slight but permanent overventilation.

TABLE IV  
URINE MEASUREMENTS  
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Volume.....	N or >	<	N or <	N	<
Elimination .....	N	<<	<	N	<<
Albumin.....	O	+	O	O	+
Casts.....	O	+	O	O	+
Sugar.....	Rarely*	Rarely*	+	O	+
"Indican".....	N	>	>	N	N
Epithelial Debris.....	N	>	>>	N	>
"Urobilinogen".....	+	O	O	O	O
Nitrogen Elimination.....	N	<	<	N	<<
Residual Nitrogen.....	N or >	>>	N or >	N	>
Phthalein Elimination.....	N	<<	<	N	<<
Salol Elimination.....	N	< or <<	<	N	<<
Urea Curve.....	N	N	N	N	<<
Urea Index.....	N	N or <	N	N	<<

\*Glucose. See text.

*Volume.* Waiving all controversial discussion of causative factors, it is a matter of record that normal or increased urine volume is the usual finding in all functional levels of pituitary disease.

Thyroid failure depresses the volume and may produce an oliguria. The condition is manifest in all the functional stadia. Patients with ovarian failure show low normal values or those even below this somewhat elastic limit. This is not a result of sex habit as the female pituitary cases do not show it. The testicular failure shows a normal volume. Lowered adrenal activity exercises a marked depressing effect at least equal to that shown by thyroid failure.

*Elimination.* This is gauged somewhat uncertainly from joint consideration of the volume and the specific gravity. Pituitary cases are normal, the bulky urines indicating a hydruria rather than a true polyuria.

The thyroid patients show poor elimination even at the increased metabolic levels of hyperfunction.

Ovarian failure determines a fair level of elimination which falls between those of pituitary and thyroid disease. The male gonad patients are normal. In adrenal failure there is marked depression which is attributable in part to the real renal impairment associated with this condition.

*Albumin and Casts.* These evidences of renal involvement are certainly associated only with thyroid failure and dysfunction, and adrenal failure. Less certainly, patients with hyperpituitarism exhibit these evidences of kidney disturbance. The implications of a possible association have already been noted (See blood pressure). While the end results are the same, the thyroid evidences of renal disease seem to rest on a "pseudonephritis" (3), while the adrenal data come from a true nephropathic condition.

*Glycosuria.* The presence of sugar in the urine opens up an interesting and important chapter in the metabolic influences of the endocrine group. Discussion will be curtailed here as the whole question is being discussed elsewhere (11). The facts are too pertinent, however, to be passed over without some mention.

Glycosuria is a most infrequent finding in an established pituitary failure. Where observed it may derive from an intercurrent non-endocrine condition, or possibly, at times, be a residual effect of an earlier over-active posterior lobe. As is well known, increased sugar tolerance characterizes failure of this lobe, and in the cases of this series showing glycosuria, there was a uniformly raised tolerance for galactose, the sugar used for testing. The metabolism of glucose and galactose are not identical, however, and in this fact may lie the explanation. It may be enough here to repeat that a glycosuria—which is always very slight—is a most infrequent accompaniment of pituitary failure.

Just as pituitary failure raises sugar tolerance, so does that of the thyroid but in much less marked degree. A priori, one would anticipate a freedom from glycosuria in this condition as well. Actually, it is occasionally observed though with a marked infrequency. Hepatic dysfunction has been shown to be a fairly common complication of thyroid failure, and to this latter influence may be traced a large portion of the recorded glycosurias. Residua of dysfunctional conditions patently account for some of them. A third and tentative suggestion has been discussed elsewhere (3).

Slight glycosuria is a common finding in ovarian failure; the testicle is without influence on the sugar metabolism in adult years.

Glycosuria is a very common finding in adrenal failure and a marked lowering of sugar tolerance the apparent background. This runs counter to the usually proffered dictum that adrenal failure raises sugar tolerance



but the customary basis for this opinion rests on a post hoc propter hoc argument involving the influence of suprarenin on blood sugar levels. Actually, the cases of Addison's disease show a profoundly depressed sugar tolerance and equally a slight and persistent glycosuria.

Since the usual type of pituitary dysfunction is that characterized by posterior lobe overactivity, it follows that glycosuria is a frequent observation in this condition. With less frequency it is recorded in cases of thyroid dysfunction for the reasons noted above. Hyperfunction of both glands frequently is associated with a slight persistent glycosuria. As the sugar tolerance in both is depressed, greatly with the pituitary, significantly with the thyroid, such a condition is to be anticipated.

For a discussion of the non-endocrine causes of glycosuria, the reader is referred to the paper just cited (11).

*"Indican."* The amount of this indoxyl derivative is usually regarded as a rough index of the degree of intestinal putrefaction. The constipated subjects of thyroid or ovarian failure frequently show an increase, and it is also noted less frequently in hyperpituitarism and thyroid dysfunction.

*Epithelial Debris.* While squamous cells and other epithelial detritus are always to be observed in the urine sediment, increased amounts are found in both thyroid and adrenal failure and even more strikingly in hypofunction of the ovary. The dysfunctional thyroid case is similar to that with failure.

*"Urobilinogen."* The presence of this pigmentary body in the urine has been primarily associated with hepatic disease. The color test for its identification is probably not specific for a single chemical entity. A positive response is frequently shown in pituitary disease. Its appearance with the other endocrinopathies is directly traceable to the presence of an intercurrent condition of which hepatic dysfunction and primary anaemia are the most significant.

*Nitrogen Elimination.* Determination of the total amount of nitrogen in the 24-hour urine serves several essential purposes. It is the one sure index of the actual level of protein catabolism, a physiological factor influencing profoundly a variety of functional levels. No wholly just interpretation of a patient's basal rate is possible without the check given by a knowledge of the daily protein utilization. It is an essential objective check on the truth of professed dietary restriction, and a settled asthenia may find its cause in a protein metabolism below a maintenance level (12), a condition far more common than is generally recognized.

Patients with pituitary failure and, of course, testicular deficiency, show a normal nitrogen output. Of the remaining three, all show a lowering which in the case of the ovarian failure is in part traceable to dietary considerations. The thyroid patient may have a poor appetite but failure to absorb is also a presumptive factor. The asthenic adrenal case marshals all of the inhibiting agencies, including some measure of retention, as these latter show uniformly a poor elimination of very real degree. With

the thyroid only the hyperfunctional level with its selective influence on protein catabolism shows a normal elimination.

*Residual Nitrogen.* As the writer has shown, the residual nitrogen fraction in the urine of patients with endocrine disease—and a number of non-endocrine conditions—shows a definite tendency to exceed those limits first defined by Folin's (13) fundamental studies. He has further shown (14) that this derives not only from increase in substances normally present in small amount in the urine, but also from the presence of nitrogen containing substances of unknown origin and composition. Due care must be taken to consider the total output of nitrogen, as the fraction is apparently a summation of endogenous materials not primarily dependent on the nitrogen intake and so it shows a rising percentage with falling nitrogen elimination. The boundary adopted is applicable when the total nitrogen exceeds 5 grams, a level determining a very definitely inadequate protein exchange.

In pituitary failure a normal value is frequently encountered although the percentage showing an upward tendency is appreciable.

Thyroid failure is characterized by values superior to the upper normal limit and may reach large degrees of excess. The same is true of adrenal failure though only in the later stages of Addison's disease do the values obtained exceed in amount those of hypothyroidism. The ovarian case simulates the pituitary although the percentage of normals is slightly less. The testicle seemingly does not influence this factor, the usual recorded level being wholly within normal limits. At the upper function levels the pituitary shows an increased tendency toward higher values which in the hyperfunction group becomes a confirmed super-normal elimination. How far the complicating renal condition—which independently may cause a high residual—is responsible, can not be said at present. With the thyroid patients the upward tendency in both frequency and degree becomes more pronounced and reaches a maximum at the clear-cut hyperfunctional level.

*Phenol-Sulphone-Phthalein.* The high hopes held at the time of its introduction for the specificity of this test have unfortunately not been realized.

Failure of the pituitary and of the testicle do not depress elimination to any characteristic extent, but the similar function level of both the thyroid and adrenal exercises a definite downward influence. Ovarian failure falls in an intermediate position—a downward tendency being manifest but not pronounced. At the upper levels of function the thyroid shows a normalizing tendency which becomes established in the hyperactive state.

*Salol.* The test is very rough and primarily indicates the degree of permeability of the kidney. It agrees with the results already noted for the "phthalein" test.

*Urea Curve.* This derives from the administration of a test meal of pure urea and the estimation of the urea output for one two-hour period

before, and four after ingestion. Delayed elimination and retention are shown very clearly by the test. Those cases with failure of the pituitary, testicle, and ovary, tend to show approximately normal curves. The point of real interest rests in the fact that the thyroid case with other evidences of kidney impairment here shows a normal picture, while the adrenal case with a true nephropathic condition shows very real retention.

*Urea Index* (15). This datum is an embodiment of the substance though not the form of the MacLean index. In the main it follows the indications of the urea curve. An interesting departure is found in thyroid failure where the somewhat high blood urea values (see later) exercise a downward tendency on the arithmetical expression of the coefficient. The adrenal lowering is a real evidence of the retention conditioned by the renal state in this disease.

TABLE V  
BLOOD CHEMISTRY  
ENDOCRINE HYPOFUNCTION

Observation	Pit	Thy	Ov.	Tes.	Adr.
Non-protein Nitrogen..	N	>	N	N	>
Urea Nitrogen .	N	>	N	N	>
Uric Acid .	>	N	N	N	>
Creatinin.....	N	N	N	N	N
Residual Nitrogen.	N	N	N	N	>
Sugar .	N	Low N	N	N	<

For a number of reasons that need not be considered here, discussion is limited to but a few of the many substances that go to make up this highly complex mixture.

*Non-Protein Nitrogen.* As an index of the amount of circulating nitrogen, the summation of the many products of both anabolism and catabolism, this quantity is highly important. In interpreting the values due consideration must be given to the level of protein metabolism as shown by the urine nitrogen. Variations in the latter will produce similar although smaller changes in the the former (unpublished data).

The patients with pituitary and gonad failure show normal levels; those with thyroid and adrenal hypofunction, a moderate increase above the normal. This statement, of course, must be modified in the terminal phase of Addison's disease, in which the total picture of the blood nitrogen reflects the grave renal condition which coexists. Patients with thyroid dysfunction show a moderate upward tendency but the hyperfunction case manifests an opposing influence and the levels recorded are apt to be low in relation to the level of protein metabolism. The high values in hyper-pituitarism are referable to the kidney condition already noted and which remains to be proven a characteristic feature of the condition.

*Urea Nitrogen.* This fraction commonly shows the same fluctuations as does the total nitrogen. The sole exception is in thyroid disease in which the dysfunctional group is as apt to be normal as to follow the upward trend of the total nitrogen, and in hyperfunction where urea is normal and non-protein nitrogen low.

*Uric Acid.* Of the hypofunctional group only pituitary and adrenal cases show an increase in uric acid above the normal. In the first it is seemingly the expression of a specific influence of the gland on some phase of purin metabolism. In the second it is merely one more evidence of an existing nephrosis. The consistently normal picture of the blood nitrogen in gonad failure, the equally consistent increase in all factors in adrenal disease, the high uric acid coupled with other normal values of pituitary hypofunction, and the directly opposite condition in hypothyroidism, form a really significant group of differential findings. High uric acid persists in all levels of pituitary disease and remains normal throughout the thyroid groups.

*Creatinin.* The values are normal throughout.

*Residual Nitrogen.* Just as summation of the several nitrogen-containing constituents in the urine shows a residual fraction to be accounted for, so in the blood a like procedure demonstrates an undetermined portion. Further, while the urine fraction is a very modest proportion of the

TABLE VI  
BLOOD MORPHOLOGY  
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Haemoglobin.....	N	Low N	N	N	<
Erythrocytes.....	N	< sl.	< sl.	N	<<
Color Index.....	N	N	N	N	>
Leucocytes.....	N	N	N	N	N
Polymorphonuclear Neutrophiles....	N	N or <	N or sl. >	N	<
Lymphocytes.....	> or N	>	N or >	N or >	>>
Eosinophiles.....	> or N	N	N	N	>
Endothelial Leucocytes.....	N or <	<	N	N	N

whole, in the blood it is second only to urea in amount and may be 40 per cent or more of the total. Only in adrenal disease does this value exceed the normal, and an equally unique finding is the low value in hyperthyroidism. The relationships throughout the thyroid and adrenal groups of the blood and urine residual fractions offer additional support to the thesis that the kidney change in thyroid disease is apparent, and in adrenal failure, real.

*Sugar.* The importance of this constituent in the diagnosis and treatment of diabetes has focussed scientific attention, and a vast literature, recording and polemical, is the result. None of the many moot questions may be considered with propriety at this time. Pituitary and gonad

failures are associated with normal levels, thyroid failure produces a moderate downward tendency but the values remain within conventional normal limits and only adrenal disease is consistently associated with levels below the normal. This latter fact is a diagnostic point of significance.

*Haemoglobin.* Normal values are associated with pituitary and gonad failure, low normal with hypothyroidism, and only adrenal disease consistently determines values suggesting anaemia. Hyperthyroid patients show normal levels and those with pituitary overactivity may exhibit high normal values.

*Erythrocytes.* The red cell count in pituitary and testicular failure is normal. Ovarian hypofunction conditions a slight downward tendency that is not to be referred to a sex influence. With the thyroid failure there is also a downward tendency which parallels that of the haemoglobin. Adrenal failure determines a lowering of the number of the red cells which is even more pronounced than that of the haemoglobin. Pituitary hyperfunction is associated with a slight upward tendency to the erythrocyte count which follows that of the haemoglobin.

*Color Index.* The fluctuations of this quantity can be predicted from those of the two foregoing factors of which it is an arithmetical expression. The values remain normal with the sole exception of those in adrenal failure, where the fall in the erythrocytes exceeds that of the haemoglobin and produces an index approaching if not equalling 1.00.

*Leucocytes.* The values drawn from some 4,000 cases show prevailing normal averages throughout. Abnormality usually derives from some intercurrent condition.

*Polymorphonuclear Neutrophiles.* Normal values prevail in pituitary and testicular failure though an occasional high percentage is found in the former. Thyroid values are normal or depressed; ovarian, normal or slightly increased. The adrenal failures show the most definite relative decrease. Higher values are shown in pituitary dysfunction, and yet higher in hyperfunction. The same trend is shown by the higher thyroid levels but it is less marked in frequency and amount.

*Lymphocytes.* This division of the formed elements seems most susceptible to an endocrine influence. In pituitary failure a slight relative increase is usually found though many of the blood pictures are normal. Both ovarian and testicular failure are usually normal but both may show increase, the latter another of the rare instances of departure from the normal in the male hypogonad. A definite lymphocytosis prevails throughout the thyroid group and to an even more marked degree and extent in cases of adrenal failure. Pituitary dysfunction shows a tendency toward lymphocytosis more strongly than at the other function levels.

*Eosinophiles.* Pituitary failure and dysfunction show a slight eosinophilia, and a similar condition is found among the adrenal cases. A possible tendency in the dysfunctional thyroid group is scarcely significant.

The other blood elements do not need discussion.

In the next table are considered the data from two independent tests. These are dealt with together because their joint indications, from the directional and quantitative standpoints, are of the greatest significance in endocrine diagnosis. The observations in question are the so-called basal metabolic rate, and the assimilation limit for galactose.

Before passing to the discussion, stress may be laid on the difficulty in securing a true basal rate and the necessity for so doing if the record is not to be harmfully misleading. Many pages could be written on this point but space forbids.

The second test has been described elsewhere in detail (16) and needs no discussion here.

TABLE VII  
BASAL METABOLISM AND SUGAR TOLERANCE  
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Basal Rate.....	<	<<<	<	N or < sl.	<<
Sugar Tolerance.....	>>>	N or >	<<	N	<<<

HYPERFUNCTION

Observation	Pit.	Thy.
Basal Rate.....	>	>>>
Sugar Tolerance . . .	<<<	N or <

Pituitary failure lowers the basal rate, and in severe uncomplicated cases may reach a level of about 25 per cent below prediction. As is well recognized, failure of the thyroid produces a change, like in direction but far greater in amount. Values for this datum of —60 per cent have been recorded though needless to say the average case of hypothyroidism will fall significantly short of this greatest magnitude. The ovary exercises an influence identical with that of the pituitary in direction and about the same in magnitude. A considerable series of castrates reported elsewhere (4) ranged from —7 per cent to —23 per cent with a group average of —14 per cent. When the disturbing effect of nervous instability on the basal rate is considered, the values will be seen to compare well with the pituitary group who are less susceptible to this disturbing outside effect.

If the testicle in adult years has any direct influence on the level of oxygen requirement, it is at best a very slight one. A series of male castrates gave an average depression of —8 per cent, and the lowest of the composing members was but —11 per cent, certainly not an index of significant hypofunction. Adrenal failure, as indicated by proven Addison's disease, produces a lowering of the basal rate more significant than that of pituitary failure but falling far short of the levels which the thyroid

can produce. Values in the minus thirties are recorded in severe cases. That the asthenia of the condition and its influence on appetite play some part in the production of the lower figures would seem to be certain. As these factors are characteristic of the disease state, the basal levels may be regarded as equally characteristic. Only the two limiting conditions need be considered as the dysfunctional states are merely algebraic summations of the opposing influences.

Hyperfunction of the pituitary is associated with a directional influence opposite from failure and of relatively the same moderate amount, +35 per cent approximating the upper limit of genuinely basal measurements.

Overactivity of the thyroid likewise produces an increase in the basal rate and this is usually about the same in relative degree as the depression of thyroid failure. Values above +100 per cent are recorded with a relative frequency. The writer's maximum value, made under basal conditions, is +87 per cent, and this phase of thyroid activity is less well represented in his series than are the other functional levels.

Turning to the sugar tolerance, a series of equally informative quantitative and directional differences are observed. Pituitary failure (posterior lobe) raises the assimilation limit for sugar far higher than does any other condition known to the writer. Upper levels of +300 per cent have been noted, the relatively small normal dosage of galactose permitting the measurement of such massive increases. Thyroid failure produces an upward tendency but it is never pronounced. Roughly, two-thirds of the cases will show a normal tolerance, and in patients with failure and uncomplicated by established renal disorders, such increases as are recorded are of the order of +25 per cent to +50 per cent. The average deviation for a long series of those showing increase is +33 per cent. Ovarian failure (or castration) lowers sugar tolerance at most to 20 grams, the prepubertal level. Of the several hundred cases in this series none has shown a level lower than this unless in the presence of some intercurrent and unrelated disease condition itself capable of influencing sugar metabolism.

Removal of the testicles in adults years has no influence on the uniform assimilation limit shown by the healthy male throughout his life, and functional failure is equally without influence. Adrenal failure, on the other hand, lowers the assimilation limit of galactose to a very marked degree, and in some cases a dose of five grams is enough to produce a definite melituria in an otherwise sugar-free patient.

Hyperpituitarism lowers the assimilation limit for sugar as markedly as failure raises it. It seems probable that the quantitative level of the tests discussed in this section are relative indices of the degree of the severity of the involvement. In long-continued observation in individual untreated pituitary cases the writer has been able to trace the gradual transition from initial overactivity to a final complete failure as shown by the galactose tolerance in connection with repeated comprehensive studies of other indices.

Hyperthyroidism affects sugar tolerance in opposite sense and usually in like degree as glandular failure. Occasionally a case is observed in which, however, a really significant depression of the sugar tolerance is found in this condition. The fact has been discussed elsewhere (3).

The discussion of the several non-endocrine influences that may simulate or confuse the individual endocrine picture must be reserved for a later communication.

One very definite possibility for confusion within the endocrine group comes in the two conditions of ovarian failure and that most common type of pituitary dysfunction in which the anterior lobe is under-active while the posterior lobe over-active. To clarify discussion and emphasize alike the similarities and divergences, data from two synthesized representative cases may be briefly presented.

TABLE VIII  
PITUITARY DYSFUNCTION AND OVARIAN FAILURE

	<i>Pituitary</i>	<i>Ovary</i>
Sex .....	Female	Female
Age .....	31	31
Weight Deviation .....	+30%	+20%
Lung Volume Deviation.....	-10%	-10%
Basal Rate Deviation.....	-18%	-18%
Temperature .....	98.2°	98.2°
Pulse .....	66	78
Respiration .....	15	15
Blood Pressure, Sys. ....	116 mm.	102 mm.
Blood Pressure, Dias. ....	76 mm.	70 mm.
Alveolar CO <sub>2</sub> .....	45 mm.	37 mm.
Urine, Volume .....	1300 cc.	1000 cc.
Specific Gravity .....	1.018	1.013
Albumin .....	0	0
Casts .....	0	0
Sugar .....	+	+
Indican .....	N	>
Urobilinogen .....	+	0
Total Nitrogen .....	11.00 gm.	8.00 gm.
Residual Nitrogen .....	8.3%	8.3%
Non-Protein Nitrogen .....	33 mgm.	33 mgm.
Uric Acid .....	4.0 mgm.	3.2 mgm.
Sugar Tolerance .....	-50%	-50%
Haemoglobin .....	93	92
Lymphocytes .....	38%	29%
Eosinophiles .....	3%	1%

A cursory survey of the table shows that the real points of difference are pulse, blood pressure, alveolar carbon dioxide, urobilinogen, total nitrogen, blood uric acid, lymphocytosis, and eosinophiles. Patently, two such cases would offer no difficulty in their differentiation but the elimination of some of the more distinctive features as, for example, the urobilinogen and alveolar carbon dioxide, might leave the conclusion in doubt. Such a condition is not uncommon, and in such case the facts of the history and physical examination furnish most valuable differential data. Finally, again these may fall short of sharp definition and a tentative diagnosis based on probability be the outcome.



By way of illustrating in a simple way the use of the foregoing data in diagnosis an ideal case of each of five uncomplicated endocrine failures may be assumed. Each patient is a young adult and the degree of gland failure is the same in each case. It must not be forgotten, however, that in the actual use of this schema, each datum must be considered in the setting in which it occurs. Ideal uncomplicated cases are the exception here as they are throughout the realm of medicine.

TABLE IX  
ILLUSTRATIVE DATA IN HYPOTHETICAL IDEAL CASES

	Pit.	Thy.	Ovary	Test	Adr.
Basal Rate .....	-25%	-45%	-18%	-6%	-35%
Pulse .....	68	50	78	72	76
Respiration .....	14	10	16	15	15
Temperature .....	98.2°	97.0°	98.2°	98.4°	97.8°
Blood Pressure, Sys. ....	110	100	98	112	90
Dias. ....	70	60	65	75	60
Sugar Tolerance .....	+100%	±0%	-50%	±0%	-83%

### SECTION III

#### *Special Examinations*

The purpose of this group of observations differs from that of the two preceding but rather in emphasis than in content. While the earlier considerations were devoted to the establishment of an endocrine diagnosis, always be it remembered, only after non-endocrine causes had been eliminated, the present group deals with data primarily significant in demonstrating the presence or absence of complicating conditions of non-endocrine origin. Only occasionally and secondarily do these evidences bear directly on the establishment of an endocrine diagnosis. For reasons which will be obvious, the present brief discussion must be limited to these latter, adequate treatment of the entire field being reserved for later communication.

*Eye Examination.* As noted earlier in the text this is now a part of the routine examination of every case. Yellowish to yellow discs are found in one-half of the pituitary cases, and with less but significant frequency in those with ovarian failure. Enlargement of the blind spots is most frequently reported in adrenal disease, next in the pituitary group, and with significant frequency in the thyroid and ovarian cases and in a large group of non-endocrine disorders.

Contraction of form and color fields of various patterns are associated with both endocrine and non-endocrine conditions. Temporal cutting with pituitary tumor is but one of several and certain of these dealing severally with: (a) cutting of the upper quadrant of the form fields, (b) concentric contraction of form and color fields, and (c) the field changes in pregnancy are shortly to be discussed elsewhere by the writer and his associates (17).

*Barany Test.* Positive findings have been reported in several cases of thyroid failure complicated by hepatic dysfunction (18).

*Electrocardiogram and Heart Examination.* In spite of the well-established influence of thyroid disease on cardiac rhythms, the proven incidence of cardiac disease associated with thyroid failure is significantly less than with either the pituitary or gonad groups (19). Further, the total endocrine incidence is much less than in the complementary non-endocrine series.

*Gastric Examination.* This consists both of the analysis for free acid and of the neutral red test. One case of Addison's disease gave no free acid and failed to show the dye at the end of two hours. Primary anaemia was ruled out. A single case is not significant but the fact is reported for a possible later interest.

*Liver Function Test (McClure)* (20). This test is chiefly interesting for its demonstration of hepatic dysfunction in a fairly large number of cases of thyroid failure (3).

*Pelvic Examination.* The demonstration of pelvic hypoplasia as a possible stigma of earlier endocrine disease, of genital abnormalities and of gross ovarian disease are the principal features of glandular significance. A very low incidence of organic ovarian change coupled with the impressive record of functional derangements is the most significant fact elicited.

*Orthopedic Examination.* The findings are directly significant for the endocrine group only in the delineation of developmental defects possibly attributable to glandular disorders.

*Psychometric Examination.* A notably high relative incidence of feeble-mindedness was demonstrated in the thyroid group. The remaining endocrine cases were associated with pituitary disease.

*Psychiatric Examination.* A significant number of endocrine patients were demonstrated to have a psychosis. The question of interrelationship cannot be considered here.

*Neurological Examination.* The simulation of endocrinopathy by various types of nervous disease is one outcome of this phase of study. The principle return is the specific significance to the individual case.

*Roentgenological Examinations.* (a) *Skull.* Enlarged diploic veins and marked convolution impressions are most frequently found in the pituitary group, though well represented in all of the others. Their suggestion of intracranial pressure are significant in a possible direct influence on pituitary activity.

(b) *Sella.* In the delineation of this structure so intimately connected with one of the ductless glands, one would initially assume a direct and important association. Further consideration, however, lessens the potential significance in view of the fact that but a small percentage of functional aberrations are associated with tumor growth. When further the amply supported fact is considered that bony structures associated with functionally normal glands are not sharply delimited as to shape or size, the real significance of the finding resolves itself into the demonstration of actual destruction of bone with the associated inference of glandular hyperplasia. An appreciable number of the pituitary cases show

abnormalities of the sella, some with erosion and some with clinoid bridging, the latter not a normal finding but equally not explicitly defining disease of the gland.

Further, in the examination of a series of 250 non-endocrine patients, 8 showed bridging, 9 a thickening of the clinoids, and 2 were reported with "notably small" sellae.

It would seem fair to deduce from these facts (and from uniformly confirmatory evidence drawn from the results of much larger series) that reliable evidence of clinoid erosion is very significant, and depending on the site involved, indicates either pituitary or extra-sellar tumor. Beyond this clear-cut indication but little specific information derives from radiographic study of the structure.

(c) *Pineal*. The observation of calcification of this structure is a by-product of the radiographic study of the head. The phenomenon has been observed in endocrine (1.6 per cent) and non-endocrine (1.8 per cent) cases alike. In none of them either in history, physical examination, or laboratory study was evidence forthcoming of those departures from the normal attributed by some to functional aberration of the gland. Like the more widely exploited structure, the testicle, objective evidence of significant endocrine activity in adult years is lacking.

The numerous other evidences from radiography deal with non-endocrine conditions and are valuable only for the individual case. An exception may be noted in the case of pyelograms.

This paper, itself a summary, cannot be condensed to a few conclusions. One point may be touched upon, however. The underlying principle of the study is not limited to the differentiation of the endocrinopathies themselves as a whole but one small chapter in the huge book of medicine. It is and should be applicable to the whole field of the diagnosis of disease, a prerequisite to, and primary step in, the determination of judicious and effective treatment.

Before the final word is written, a brief statement should be made. This paper concludes a series of reports which are the first formal presentation of studies begun in 1912 and prosecuted without remission ever since. In the compilation of the data, many thousands of records have been made ranging from single individual chemical analyses to the series of lengthy and carefully conducted interviews which furnish the basis of a psychiatric report. All of this material represents the accurate, sincere, interested labor of a large group of highly trained individuals. To them all, laboratory and clinical assistants, associates and colleagues, the writer can but acknowledge an indebtedness and an inspiration that cannot be expressed.

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# GEOGRAPHICAL FACTORS IN CALCIUM METABOLISM\*

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At this time I wish to call attention to the possible causitive relationship between blood calcium deficiency as a clinical entity and calcium deprivation; also to report the results of blood calcium determinations on clinical subjects. Further, I wish to point out certain geographical factors which undoubtedly bear on the question of calcium metabolism in the State of Washington.

## BLOOD CALCIUM

The method of determining blood calcium was that of Clark and Collip's modification of Tisdall's technic (1).

Blood calcium determinations were made on 425 partially selected young adult and adult men and women. The average calcium content per 100 cc. of blood for the series was 10.34 mgm. Individual readings varied 12.6 mgm. (4.0-16.6 mgm.). Of the total number, 78 (18.33 per cent) had calcium readings of less than 9 mgm., 286 (67.28 per cent) had readings of 9 mgm. and above and below 12 mgm., and 61 (14.34 per cent) had readings above 12 mgm. (Table 1.)

The average figure of 10.34 mgm. for this series of determinations closely conforms to the usually accepted normal average of 10.0 and 10.5 mgm., the range of normal variation lying above 9 and below 12 mgm. (2 and 3).

If 9 mgm. is to be considered the minimum normal, then 18.33 per cent of the present series of patients were suffering from hypocalcemia. On the other hand, if 12 mgm. is to be considered the maximum of normal variation, then 14.34 per cent of the series were suffering from hypercalcemia. In other words, if the figures for blood calcium as given by others are accepted as normal, then 32.67 per cent of the present series of patients had varying degrees of disturbance in their calcium metabolism.

The average figures for the present series coincide with figures obtained elsewhere, but the extremes of variation are greater than those reported for other locations. Because of this and a study of the numerical distribution of calcium readings (Table 1) I am inclined to place the lower normal level of blood calcium at 8.5 mgm. (4) and the upper normal level at 12.4 mgm. If these figures are accepted as normals, then 39 (9.17 per cent) of the present series had calcium readings which were definitely below normal and the same number, namely 39, had readings above normal.

\*Read before The Association for the Study of Internal Secretions, Portland, Oregon, July 9, 1929.

That is, 78 or 18.34 per cent of the total number of 425 were characterized by abnormal variations in their calcium level.

TABLE I

SUMMARY OF BLOOD CALCIUM DETERMINATIONS IN 425 PARTIALLY SELECTED CLINICAL SUBJECTS

Mgm. per 100 c.c. of blood	No. of tests	Per cent	No.	Per cent
4	4	0.93	39	9.17
5	2	0.47		
6	4	0.94		
7	10	2.35		
8-8.4	19	4.47		
8.5-8.9	39	9.17	347	81.65
9.0-9.4	47	11.05		
9.5-9.9	40	9.41		
10.0-10.4	56	13.17		
10.5-10.9	57	13.41		
11.0-11.4	55	12.94		
11.5-11.9	31	7.29		
12.0-12.4	22	5.17	39	9.17
12.5-12.9	14	3.29		
13	13	3.07		
14	7	1.65		
15	1	0.23		
16	4	0.94		
TOTAL	425	100.00		
AVERAGE.....		10.34 mgm.		
VARIATION.....		12.6 mgm. (4.0-16.6 mgm.)		

This large percentage of cases showing calcium disturbances, in my opinion, is indicative of either a poor technic or that we of the Puget Sound Basin of Washington are confronted with a clinical situation which is comparable to that of the goiter problem. In defense of the technic I wish to state that it was the one accepted by Eli Lilly and Company in their pharmaceutical development of Parathormone (5). In our own work, error in individual determinations was eliminated wherever possible by running more than one blood sample at a time. Initial readings of less than 8 mgm. were rechecked before they were accepted as correct. In support of the second possibility, it may be stated that the clinical studies give support to the laboratory findings. For instance, 19 or practically 50 per cent of those patients showing a calcium of less than 8.5 mgm. were diagnosed as having spasmophilia from the history and physical findings.

These findings and the tentative conclusions to be derived from them may be open to severe criticisms. However, it remains an interesting clinical fact that 19 or 4.5 per cent of a series of 425 subjects in any given locality are diagnosable as spasmophilias from the history and physical findings alone. It is also of interest to observe that blood calcium determinations in the same series of patients reveals another 4.6 per cent possessing critical calcium levels. Of most interest to me has been the obser-

vation that of the 19 patients who suffered from spasmophilia; in only one (post-operative parathyroopriva) had the condition been recognized and treated as such.

#### WATER SUPPLY AND CALCIUM

It is well known that the water supply of the Puget Sound Basin is practically wanting in mineral elements. Goiter in this region is looked upon as the result of iodine deficiency incident to the water supply (6).

TABLE II

#### CALCIUM CONTENT OF THE RIVER WATER OF THE STATE OF WASHINGTON

River	Calcium Parts per Million
1. Skagit River at Sedro Woolly.....	7.9
2. Wood Creek near Everett.....	8.6
3. Cedar River at Ravensdale.....	6.7
4. Green River at Hot Springs.....	6.0
5. Chehalis River at Centralia.....	7.1
6. Wynooche River near Montesano.....	8.2
7. Columbia River at North Port.....	18.0
8. Okanogan River at Okanogan.....	21.0
9. Wenatchee River at Cashmere.....	5.5
10. Yakima River at Cle Elum.....	6.7
11. Naches River at Naches.....	8.2
12. Yakima River at Prosser.....	16.0
13. Columbia River at Pasco.....	18.0
14. Snake River at Burbánke.....	19.0
15. Klickitat River at Klickitat.....	7.1
16. Columbia River at Cascade Locks.....	16.0
17. Spokane River at Spokane.....	11.0
AVERAGE.....	11.2

Clarke, F. W.: *The composition of the rivers and lakes of the United States*. Bull. U. S. Geol. Survey, Professional Papers No. 135, 1924.

An analogous condition subtends for water calcium (7) (see Table 2). For instance, the average calcium content per million parts is 11.2 for the rivers of Washington. This is an extremely low figure as compared, for instance, with the average of 81 parts per million for 16 rivers of the Missouri River Basin.

A water supply deficient in calcium content of necessity occurs if the land over which the water is collected is wanting in lime. That the lands of the western slope of the Cascade Mountains are deficient in lime (8, 9) is evidenced not only by the lack of lime in the water, but also by the inability to grow repeated crops, especially clover, on our logged-off lands unless lime is artificially supplied.

#### CALCIUM DEFICIENCY AND HYPOCALCEMIA

Calcium deficiency may be looked upon either as the result of endogenous factors which prevent the utilization of an available adequate supply or because of exogenous factors or the want of an adequate supply.

The clinical results of either factor may be the same; however the problems involved in the care of each are quite different.

Thoretically, an adequate supply of calcium is available in a general diet. However, the diet of city dwellers in America is often deficient in this element (10). The amount of calcium in foodstuffs, in turn, depends upon certain factors; for instance, the amount of sunshine during the growth of vegetables, the amount of available lime in the soil and in the water supplying the soil used for the growing of foodstuffs. The calcium content of drinking water is also a factor in the supply available for consumption.

Consideration of the local geography is highly suggestive of a diminished supply of calcium for both vegetable and animal consumption. The fact that 18.33 per cent of the patients upon whom blood calcium determinations were made showed readings of less than 9 mgm. may be looked upon as clinically reflecting a low available calcium in foodstuffs and drinking water directly and the soil indirectly. On the other hand, the fact that 9.17 per cent of the patients had calcium readings which were definitely above normal (12.4 mgm.) can hardly be construed to indicate a direct deficiency in available calcium.

At the present time, I have no definite figures as to the amount of calcium in our locally grown vegetables or milk supply. However, from the above consideration I am convinced that the people of this region have but a minimal natural supply of calcium. This conviction receives some degree of rationalization because of the present clinical findings. Should it later be proved that the figures presented in this paper are correct, at least relatively, then we of this location are confronted with a clinical situation which is of geographical and geological interest and importance. That is, disturbed calcium metabolism in this region may then, in part, be looked upon as having its etiology in geographical factors.

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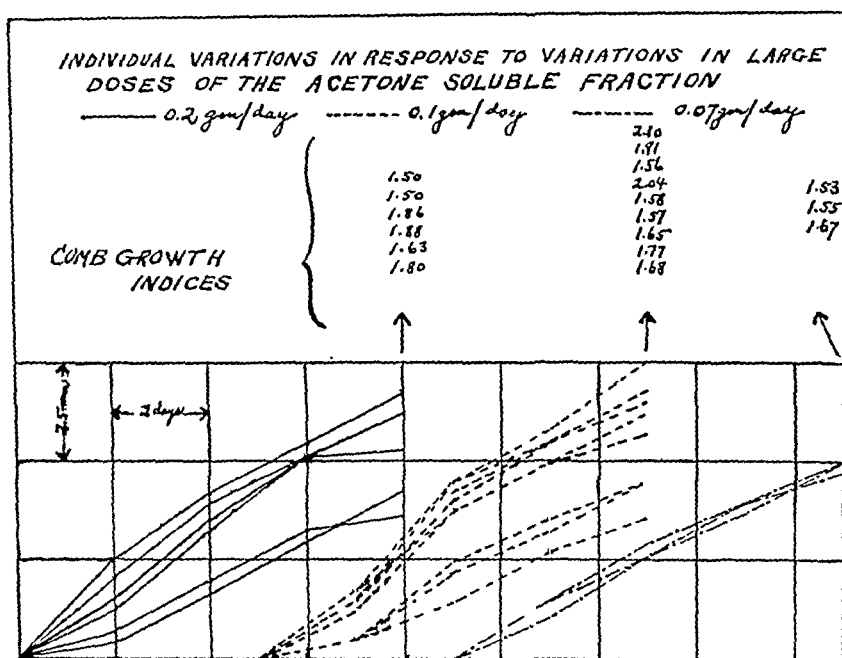
# THE EFFECTS OF EXTRACTS OF TESTIS IN CORRECTING THE CASTRATED CONDITION IN THE FOWL AND IN THE MAMMAL.\*†

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It is hardly necessary to state to this group that clear-cut experimental evidence of the presence of an internal secretion of the testes has been based primarily upon the effects observed on the removal of the testes. Although many claims have been made from time to time that extracts of testicular tissues when injected into castrated animals produced various effects, many of which were associated with secondary sex characters, it is

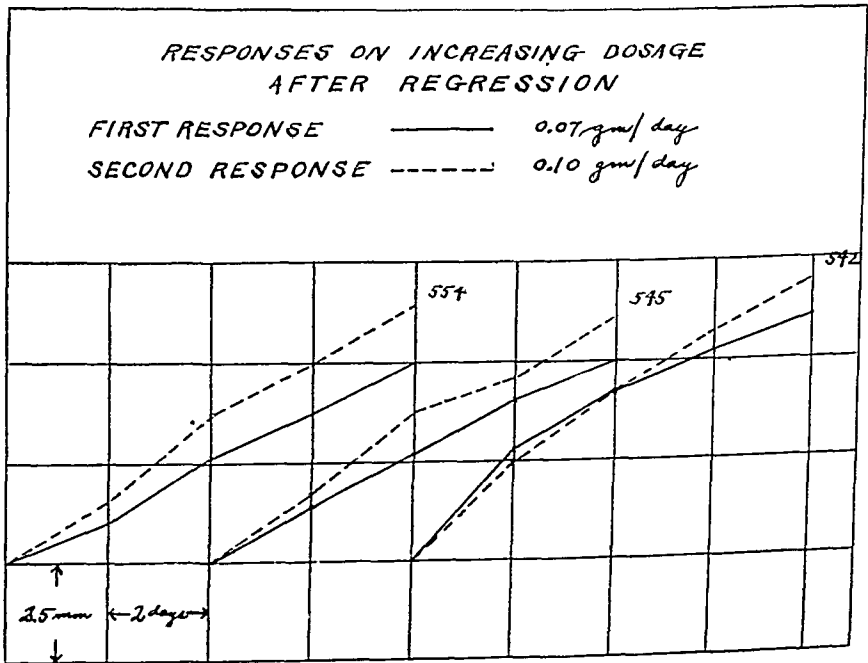
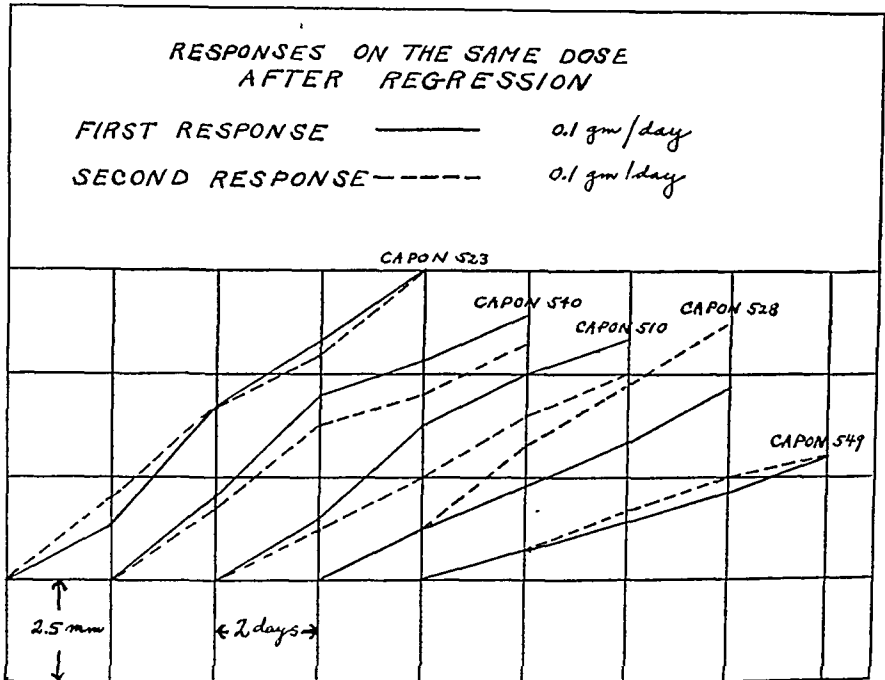


nevertheless true that most workers in endocrinology do not accept these claims in that the criteria used for detecting the effects of the extracts on the castrated animals were of doubtful value. It is our aim in the paper today to present clear-cut evidence that we have now been able to obtain a truly active extract from bull's testicles. The first observations in this connection were made by L. C. McGee and F. C. Koch as first published in 1927 (1). In these studies we observed that properly prepared extracts

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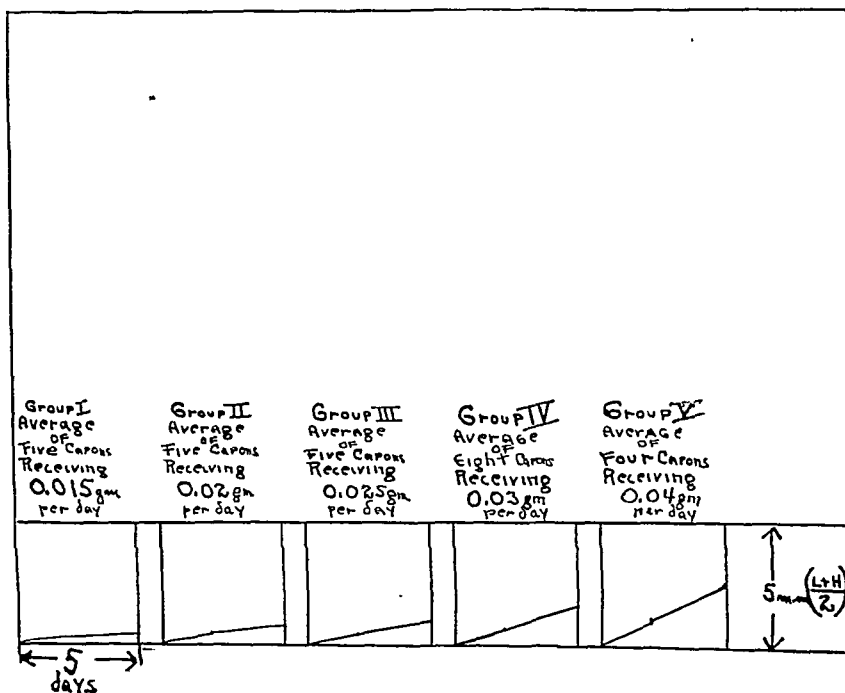
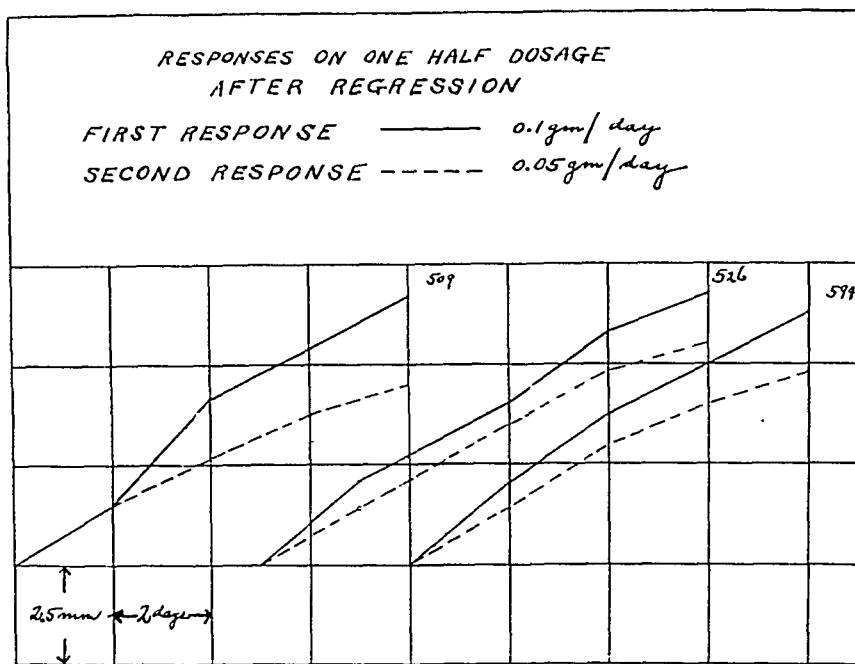
†Paper read by F. C. Koch at the Portland meeting of the Association for the Study of Internal Secretions, on July 9, 1929.

of bull's testicles when injected intramuscularly and daily into brown leghorn capons caused a remarkable growth of the comb, wattles, and ear lobes. The response is very prompt in that one can usually observe the



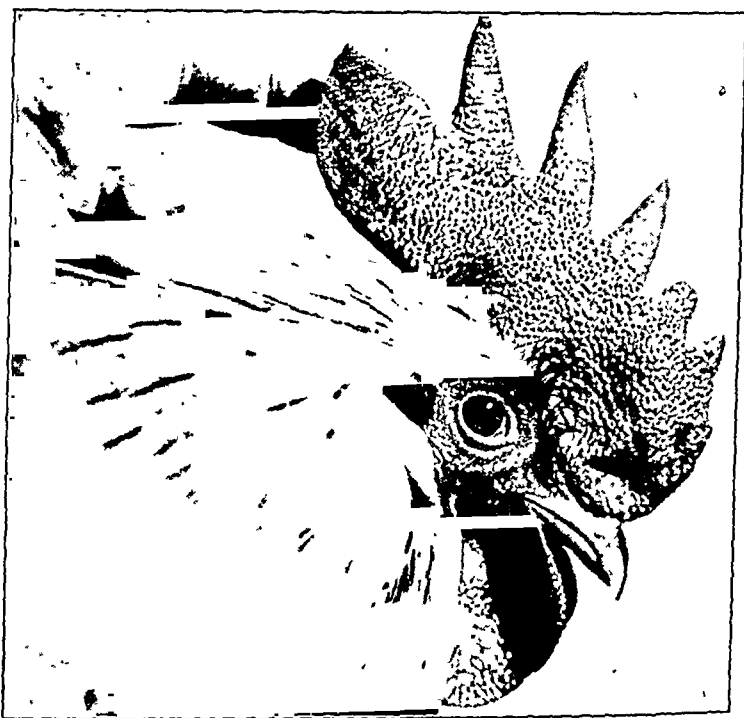
increase in size of the comb in one to three days after the first injection; and it is also interesting to note that on ceasing injections the regression of the comb to the capon type takes place very promptly. The accompanying figures illustrate the remarkable effects of such extracts.

All of us appreciate that in order to make real progress in the further purification of this activity it will be necessary to have a quantitative method for determining the amount thereof, and inasmuch as we do not



at present have chemical methods for measuring this amount we are limited to the biological effects for methods of assay. The accompanying graphs clearly show that this is an involved procedure and at best a very crude one. A careful inspection of Graph 1 shows that the responses of

different birds to a given dose are decidedly variable if the dose introduced is considerably above the minimum. Graph 2 also indicates that one and the same bird does not necessarily respond qualitatively in the same manner when tested at two successive times on the same high concentration of the same extract. Graphs 3 and 4 show that a given animal does not necessarily show a corresponding increase or decrease in growth on increasing or decreasing the dosage. These observations together with many others finally led us to the conclusion that in these studies as in so many physiological assays it is exceedingly important first to determine the minimum dose causing a measurable growth of the comb. In Graph 5 we give the average results on minimum doses and on slightly increasing doses on the capons. It is obvious here that if one determines the minimum



1. Capon 903—Photograph taken August 16, 1928. Prepubertally castrated brown leg-horn. Received 10 mgm. of preparation 48B daily for 28 days previously.

effective dose the comb growth observed will be at least a fair measure of the quantity of the active material injected.

After finding this activity in bull's testicles it at once became necessary to show that this substance is specifically present in testicular tissue and not possibly a general extractive found in various tissues. The results as published by one of us, T. F. Gallagher (2), show that this substance was not obtained by the same method of extraction from brain, pancreas, blood, prostate, thyroid, suprarenal, kidney, liver, and seminal vesicle of the bull. It has not been found in the ovary of the cow. We should add that in the negative experiments indicated above we injected the equivalent of much larger quantities of tissue than we used in the case of the testes. Thus far we have found only one other tissue to contain this activity and

that is the epididymis of the bull. The concentration in the epididymis, however, appears to be approximately one-half that found in the testicles. Since the publication of Gallagher's findings we have confirmed the same on the epididymis and we can also state that we have found this activity in the testes of the hog and calf. We have not found it thus far in the



2. Capon 903—Photograph taken August 16, 1928. Prepubertally castrated brown leg-horn. Received 10 mgm. of preparation 48B daily for 28 days previously.



3. Capon 903—Photograph taken October 10, 1928. Injections were discontinued August 17, 1928.

testes of the ram\* and white fish. It appears then that this activity is more or less specifically associated with testicular tissue.

Thus far these observations are so specifically applied to the fowl that one might consider this simply a scientific curiosity. We are, however,

\*Since the reading of this paper we have been able to demonstrate the presence of the active principle in the testes of the ram.

delighted to be able to report here that preparations found so active in the capons have actually been shown by us to correct certain castration effects in the rat and in the guinea pig. The early studies of C. R. Moore and his students on the various effects observed as the result of castration in the rat and guinea pig laid the foundation for the criteria we have been able to use in the mammalian studies reported here. Earlier observations by Benoit (3) and Moore (4, 5) showed that an intact testis, or part of a testis in situ, or a cryptorchid-testis prolongs the time of motility of the spermatozoa found in the epididymis. Whereas, it is found that in the case of a completely castrated guinea pig with the epididymides left intact, the spermatozoa never were observed to retain their motility beyond 23-25 days following castration, we have placed thirty days as the maximum time, and consider that if we can prolong the time of motility beyond that period we will have shown an activity associated with the internal secre-



4. Capon 903—Photograph taken October 10, 1928. Injections were discontinued August 17, 1928.

tion of the testes. By this spermatozoon motility test, Moore and McGee (6) have been able to demonstrate a distinct prolongation of the time of motility of spermatozoa, the longest time being fifty-four days.

The second mammalian test reported in this laboratory is the electric ejaculation test. This test, originally discovered by Battelli (7) in 1922, consists in inducing the animal to ejaculate semen by an electric stimulus through the brain. The reaction is very specific and can be applied repeatedly after certain time intervals upon one and the same animal. A normal guinea pig if thus tested once per week yields a secretion of 1.5 to 2.0 grams. This material consists of secretions from the seminal vesicles and the prostate. It is distinctly fluid as ejaculated but very soon coagulates to a firm jelly due to the coagulating enzymes present in the prostate secretion. In a castrated guinea pig, however, these secretions are no longer normal several weeks after the operation; the result is that little or no material is ejaculated when the test is applied, and whatever material is

secreted is exceedingly small in amount and does not coagulate. Moore and Gallagher (8) have shown that if a castrated guinea pig is injected with our extract we can distinctly correct the loss of secretory function of both the seminal vesicles and the prostate in that the ejaculated material is near to the normal in amount and possesses the normal characteristic of coagulation. They have even taken an adult guinea pig which has been castrated for six months and in which the ejaculation test had been found negative for some time and after ten to fourteen days' injections of our extract obtained a normal ejaculation.

The third mammalian test applied by Moore, Price and Gallagher (9) is that of the testis control on the prostate cytology. The prostate of the rat is composed of anterior, middle, and posterior lobes. In the castrated animal the entire organ usually diminishes appreciably in size but more certain and more striking still are the marked changes in the cytology. Moore, Price and Gallagher have not only prevented the degenerative changes as shown by the cytology but they have actually been able to construct an apparently histologically normal adult prostate in a one-hundred-days old pre-pubertally castrated rat by injections of our extract. In these cases varying injections over a period of twenty to thirty days were necessary. These studies in part at least are cytological confirmation of the physiological ejaculation test.

The fourth mammalian test applied by Moore, Hughes, and Gallagher (10) is that of the testis control on the cytology of the seminal vesicles of the rat. Here again it is well known that the size and cytology of the seminal vesicles are controlled by the testes. The observations on the cytology of the seminal vesicles in the castrated animal as affected by injections of our extracts are just as striking as those upon the prostate cytology.

Our studies thus far indicate that from a qualitative point of view the comb growth reaction and the mammalian cytological tests reported on here are of about the same order of delicacy. The spermatozoon motility test is approximately ten times as sensitive as the comb growth method, but the ejaculation test is the least delicate of all. The mammalian tests are at present not as suitable for quantitative assays as the comb growth method.

Finally a few remarks may be offered in regard to the chemical nature of this material. It is found in the lipid fraction and, in general, can be fractionated by methods very similar to those employed on the female sex hormone. The material is relatively resistant to temperature, acids, alkalis, and also to exposure to oxygen. The yield of the activity is exceedingly low. In our earlier studies we found it necessary to inject the equivalent of one-half to one pound of testicular tissue in order to be able to make an assay on the capon. With better methods of comb measurement and further purification of material, we have been able to observe effects from injections representing very much less original tissue. Our most

active and probably purest preparation obtained thus far is one in which a dose of 0.01 milligram of the active material per capon per day causes distinct comb growth.

We conclude from these studies that the preparations we are using at the present time contain either one substance having all of these physiological properties or different substances as the result of which we are able to bring about these changes in the capon and in the castrated rat and guinea pig.

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# THE LAURENCE-BIEDL SYNDROME

## REPORTS OF TWO CASES IN ONE FAMILY

### RESULTS OF TREATMENT<sup>\*</sup>

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In 1866 Laurence and Moon reported in *The British Ophthalmologic Review* a remarkable family group, in which four of eight children, born of healthy parents, exhibited adiposity, genital dystrophy, retinitis pigmentosa and mental deficiency. Three of these children showed, in addition, faulty muscular and skeletal development, which resulted in a disturbance of gait.

Pigmentary degeneration of the retina, associated with polydactylism, was described by Höring in 1864, and by Wecker and Stör in 1865, but no mention was made of obesity or sexual infantilism as concomitant features. The association of retinitis pigmentosa with disturbances of internal secretion was not generally recognized until quite recently. In the Bowman Lecture of 1923, de Schweinitz stated that during a discussion on Internal Secretion, at the Thirty-Fourth Congress of the *Deutsche Gesellschaft für innere Medizin* in Wiesbaden, April, 1922, "a newly established syndrome" was thus described: Congenital malformations (atresia ani, polydactylism, retinitis pigmentosa); deformities of the skull; retarded mental development; marked obesity with or without genital hypoplasia, and a peculiar form of indigestion. This clinical entity was named by Solis-Cohen and Weiss, the Laurence-Biedl Syndrome.

Two months later Elschnig, at a meeting of the *Prague Verein für Deutsche Aerzte*, demonstrated three cases of retinitis pigmentosa, which were either inherited or acquired in early childhood, and also called attention to the relation of retinitis pigmentosa to diseases of the organs of internal secretion. At the same meeting Biedl reported three cases, two of which occurred in the same family. In addition to adiposity, genital hypoplasia and retinitis pigmentosa, his cases presented polydactylism. Raab, who subsequently reported these cases more fully, pointed out the fact that out of six normal births, four of the children were affected. Two of these, who died in infancy, also had polydactylism. The two affected children, who survived, showed some mental abnormality. Both subjects responded to hormonotherapy (thyroid and pituitary); the vision improved and there was a reduction in weight. Other cases have been reported in literature, making a total of thirty-five, including my own cases.

Polydactylism was not mentioned as a feature in Laurence and Moon's cases, nor did it occur in two of Lange's cases, although, in one of these syndactylism was present. Two children with polydactylism, which oc-

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<sup>\*</sup>Reported at a meeting of The American Therapeutic Society, Pittsburgh, April 6, 1929.

curred in Biedl's family group, and one of Lange's, died in infancy and, therefore, are not included in the series.

Although the disease usually manifests itself by affecting several or more children in the same family, there is no record of the condition occurring in their ancestral relations.

Consanguinity was mentioned twice. In one family with eight children, four of whom were affected, the parents were cousins. In another family of eight children, of whom two were affected, the parents were cousins and the father's father also married a distant relative. In this family there was a history of alcoholism, epilepsy, and insanity.

The cases reported ranged from 7 to 51 years of age, and were almost equally distributed between the sexes. Most of them were familial in character and usually about one-half of the children were affected. Thus 27, including my own, occurred in 10 families. There were only 8 families in which a single individual was affected. It is a curious fact that four of the families had eight children, four of whom were affected in each family. It is further noteworthy that in three of the families two sons and two daughters were affected. In one of these families the disease syndrome occurred in the 2nd, 4th, 6th, and 8th child. In the fourth family, which consisted of one daughter and seven sons, the daughter and three of her brothers were affected. The same ratio existed in Bernhardt's report of two boys affected in a family of four children, and in my report of a boy and girl in a family of four children.

Obesity with hypogenitalism of the Frölich type occurred in almost all of the cases. In nearly all of the boys there appeared feminine characteristics in the body contour with hetero-sexual distribution of hair in the adults. In the girls, menstruation was either absent or delayed.

Polydactylism or syndactylism was almost invariably present. The extra fingers or toes were rudimentary and appeared on the outer side of the little fingers or toes. These varied in number from one extra finger or toe on one hand or foot to one on each hand and foot. In one instance the patient had six fingers on each hand, six toes on one foot, and seven toes on the other foot. The extra digits usually had been amputated in infancy so that only a scar remained. Other malformations have occurred such as atresia ani, spinal curvature, and muscular defects; owing to the latter they exhibited a peculiar waddling, or "slouching" gait.

Visual defects were constant. In a few cases they had been observed by the parents during the first year of age. However, they were ordinarily not recognized until they entered school. In many of the cases the vision seemed to be normal in early childhood, impairment manifesting itself later, in several instances as late as ten to fifteen years. Night blindness was observed in some of the patients. Nystagmus occurred frequently and strabismus occasionally. The pupils reacted sluggishly. The visual fields were often contracted. In some cases there was atrophy of the optic nerve and almost all showed abnormal pigmentation of the retina.

The affected children always showed definite mental retardation, especially when compared to the other children in the family who were not affected. These have been described in the various reports as mentally delinquent, inferior, slow, subnormal, obtuse and unintelligent, dull and inanimate, childish and apathetic, timid and emotional, markedly deficient and cheerful, stuporous, and moderately imbecile.

The laboratory studies have not disclosed any characteristic findings. The blood morphology was usually normal. The blood Wassermann reaction was negative in all cases except one, a case of inherited syphilis. Basal metabolic tests were made in only a few cases. These ranged from —3 to



1. Mother and four children. The affected children are in the center. The youngest son on the left and the oldest on the right are normal.

—29 percent. Roentgenologic studies of the sella showed, in the majority of the cases, slight abnormalities. These were related to the size and general outline. The sellas were usually smaller than normal and occasionally flattened and irregular in contour.

The patients who form the subject of this report were suffering from visual defects and were referred by their ophthalmologist, Dr. Fleck, for study. The parents were Italian. They had four children, three boys and one girl. The youngest and oldest were not affected. The mother was very short and slender, measuring four feet and eleven inches, and weighing 88 pounds. She had a slight scoliosis, bowing of tibiae, and a supernumerary molar.

The father appeared healthy and was normally developed. He was five feet and four inches in height, and his weight ranged from 160 to 170 pounds. There was no history of constitutional inadequacies and anomalies or endocrinopathies of either the maternal or paternal antecedents,

nor was there a history of consanguinity by marriage of the parents or their immediate ancestors.

The age, height and weight of the four children were as follows:

	Age	Height	Weight
Albert	14 years	5 ft. 4½ in.	103 pounds (normal)
Adolph	11 years	4 ft. 8 in.	123½ pounds (affected)
Isabella	10 years	4 ft. 7½ in.	128½ pounds (affected)
Howard	7½ years	4 ft. 0 in.	45½ pounds (normal)

Both Albert and Howard were normal mentally and closely resembled their mother in constitutional characteristics. They also possessed a marked asthenic habitus, whereas Adolph and Isabella presented entirely different morphological features and were mentally inferior.

#### CASE REPORTS

CASE I. The mother states that Adolph was delivered normally, but was born "dead" and had to be revived. He was a small child. For two years he was bottle fed on cow's milk. For the latter part of this period he ate certain food



2. Case I, age 11. Note the Fröhlich's type of obesity, feminine breasts, prominent abdomen, large mons, underdeveloped genitalia, short extremities, genu valgum, thick infiltrated integument of lower extremities, and dullness of expression.

under the direction of a visiting nurse. His weight was normal at this time. Later he began to take on fat. He talked at the age of fifteen months and walked before the age of two years. Dentition was normal. His mother states that he was a "good baby" and played with toys. Later, however, he developed a "temper" and became refractory and at times incorrigible. He was dull, apathetic, and lacked initiative.

At the age of six he entered school. He was not interested in his studies, which was attributed to his impairment of vision. During his period of five years in school, he succeeded in passing only the first grade. He was able to add and subtract and to spell a few simple words. He showed some tendency to play with boys his own age, but never took any active interest in games. His endurance was good. He was not drowsy but slept well at night. There was no his-



3. Hands of patient, Case I, showing characteristic tapering fingers, of pituitary type, and slight deformity of the right hand, which remained after the removal of the sixth digit.

tory of night terrors. Headaches, from which he formerly suffered, were relieved by glasses. His appetite had always been good. He ate 4 or 5 slices of bread with each meal and was very fond of spaghetti, potatoes, and sweets. There were no symptoms suggesting any cardio-vascular, gastro-intestinal, or genito-urinary disturbances.

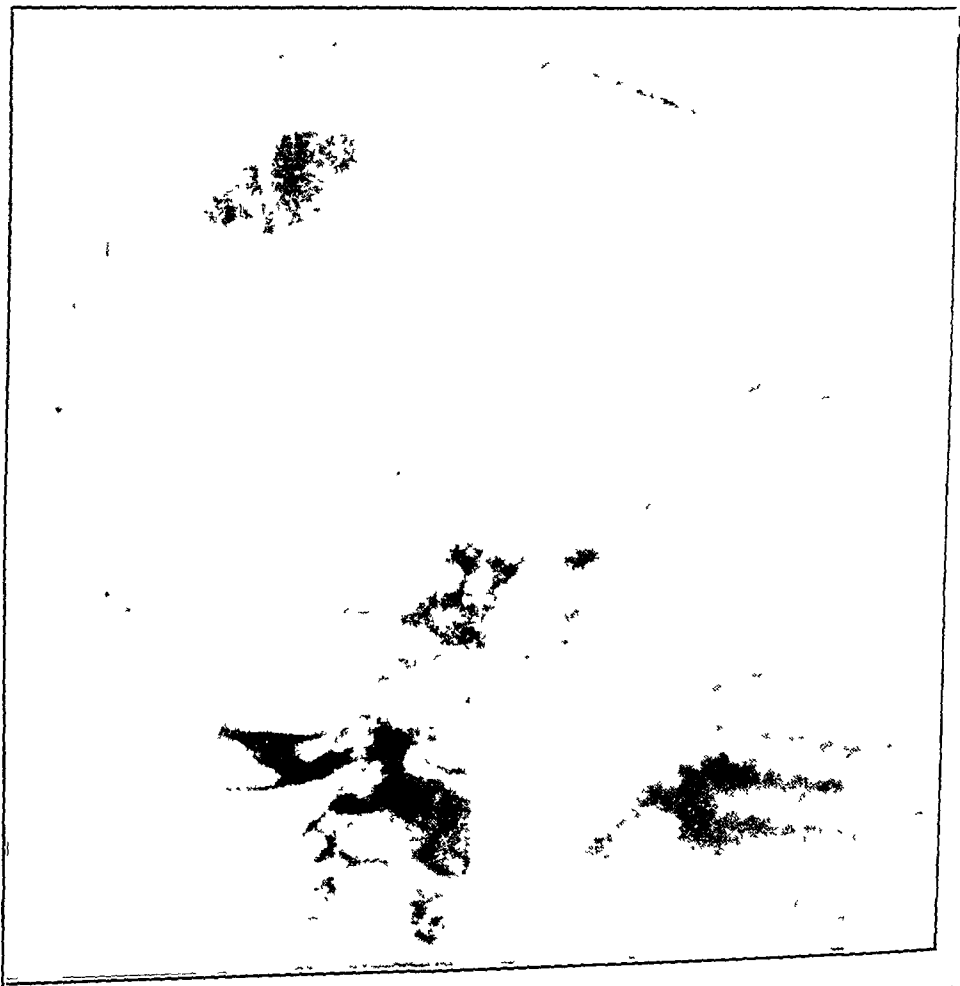


4. Illustration showing integumental changes of the lower extremities, deformity of the feet, irregularity in the size and shape of the toes, and syndactylism. (Case I.)

When the patient was examined on October 1, 1927, he presented an extreme grade of obesity, weighing 123½ pounds and was 139 cm. in height. The fat was generally distributed. His face was full and round, and he had a large double chin. He had heavy pads of fat around his shoulders, large well-developed feminine type of breasts and a prominent abdomen with marked panniculus adiposus. The mons was very large. In it the penis, which was diminutive in

size, was imbedded. The scrotum appeared normal but the testicles were underdeveloped. There were large accumulations of fat over both thighs and the calves were abnormally large.

The skin over the face, body and upper extremities was moist, delicate and soft in texture, while that of the lower extremities, especially below the knees, was dry, thick and infiltrated, resembling that of myxoedema. There was no growth of body hair, but he had a heavy suit of hair on the scalp. He also exhibited faulty skeletal growth. Both upper and lower extremities were relatively short. Genu valgum was marked. His measurement from symphysis to heel was 60.5 cm. and from symphysis to top of head, 68.5 cm. His height exceeded his span by 3.5 cm. The hands were broad and the fingers short, thick and tapering. On the right hand, opposite the last metacarpophalangeal joint,



5. Case I. Note the abnormal contour of the skull and the abnormal shape of the dorsum of the sella.

he had a scar from the removal, in infancy, of a rudimentary sixth finger. The feet were likewise malformed—short, thick and broad—so that he was unable to wear ready made shoes. From the right foot he had had a rudimentary sixth toe removed. The first and second toes were normal in size. The remaining toes were small, irregular in size and overcrowded. The two outer toes had been removed from the left foot, owing to syndactylism. The third and fourth toes were also united and diminutive in size. Both finger and toe nails were short, deformed, and extremely brittle. The skull was abnormal in contour due to flattening of the superior and posterior surfaces which gave it a rough quadrilateral outline. The antero-posterior diameter was greatly diminished, the transverse was increased. There was maxillary prognathism with a small, narrow, receding mandible. The upper central incisors were very large, and the

lateral incisors were proportionately decreased in size. The lower teeth were regular in size and distribution.

During the examination, the patient sat with his head drooping. He appeared dull and expressionless and manifested a spirit of antagonism. He presented a low forehead, scanty eye-brows, narrow lid slits, fatty eye-lids and tendency to squint. The pupils were even and reacted normally. The ears were prominent and projected outward, almost at right angles.

The nose was small and nasal breathing was obstructed. The lips were thick and prominent, and the tongue, which was thick and pale, protruded in the midline. The palatal arch was high and narrow. The tonsils had been removed. The thyroid was not palpable.

Nothing abnormal was found in the thoracic and abdominal viscera.

The knee jerks were sluggish.

The urine, blood count, and Wassermann reaction were normal. Further laboratory studies were denied because of his failure to coöperate.

The *ophthalmologic report* by Dr. Fleck is as follows: Vision is one-sixth normal in each eye. The optic nerve is partially atrophied. The arteries and veins are quite small. Both retinæ show atypical spots of pigmentation. He gives a rather definite history of night blindness.



6. Right hand of patient, Case I, showing a small center of ossification, the remains of the sixth finger, and retardation of development of the second phalangeal bones, especially the little finger.

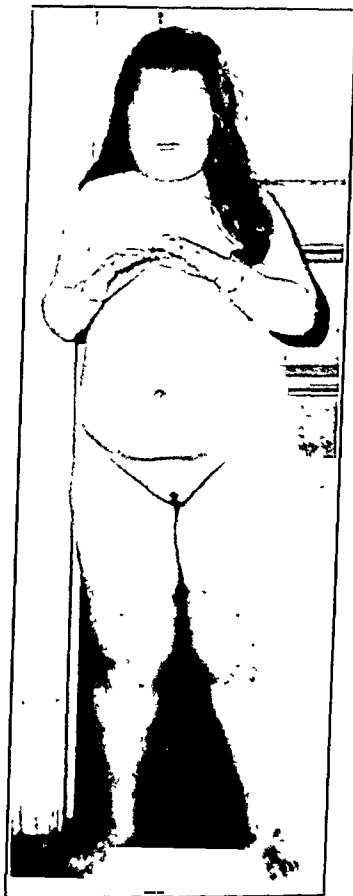
*Roentgenologic Examination:* The skull is rather large. The bones are of normal thickness and density and the sutures are normal. There is some flattening over the occipital area and the vertical diameter is increased in the posterior portion. The sella is large and regular in outline. The only abnormality is an unusually high dorsum, a feature to which Biedl directed attention.

*Hands:* In the right hand there is a small round center of ossification still remaining in the soft tissues where the sixth finger was removed. The first or proximal phalanx of the little finger and the second or middle phalanges of all the fingers show retarded development in the right hand. The left hand shows, in addition, involvement of the first or proximal phalanx of the fourth finger. The other phalangeal, carpal and metacarpal bones appear normal.

*Foot (left):* There is webbing of all the toes. This is more marked between the third and fourth toes. The phalanges of the little toe were removed with the amputation of the sixth toe. The tarsal and remaining phalanges appear normal. The metatarsal and phalangeal bones of the third and fourth toes are very much retarded in growth.

CASE II. The mother states that the patient's birth was normal and that she was of average size and developed normally during infancy. She was also a bottle fed baby and also had a rudimentary sixth finger, which was removed immediately after birth, but no extra toes. Like her brother she was fed on cow's milk, and ate practically the same diet. She likewise had a craving for sweets. Dentition was normal and she walked and talked at the usual time. At an early age she began to gain abnormally in weight. She was of a quiet demeanor, talked very little, and was more sluggish than her brother and exercised less. She was affectionate and played with other girls. At the age of seven she entered school, where she spent three years in the first grade. On account of her vision she had difficulty in reading. She was subject to headaches, which were relieved by glasses.

On physical examination she presented the appearance of being almost the prototype of her brother, especially with respect to the body configuration and



7. Case II, age 10. Note similarity of features as compared with Case I.

general skeletal development, including malformed skull, short extremities, genu valgum, pudgy hands, tapering fingers, brittle nails, etc. She weighed 128 pounds and her height was 139 cm. The obesity was of the Fröhlich type, with well developed breasts, prominent abdomen and large mons. The hips and thighs were also very large. The skin was soft, moist and delicate except over the lower extremities where it was thick, leathery and infiltrated. She had a heavy suit of hair on the head and many fine hairs on the legs below the knees. The head was abnormally large and the frontal eminences were very prominent. She had a low forehead and full round face with a double chin. She had a "peaches and cream" complexion and her expression was bright and her mood cheerful and happy. In the left eye there was a slight squint. The pupils were normal. There was a mild degree of maxillary prognathism and considerable ridging of the teeth, but the size and arrangement were normal. The tongue was thick and coated. The tonsils were not enlarged. The thyroid gland could not be palpated. No abnormalities were found of the thoracic or abdominal organs. There was no



deformity of the feet or toes other than a moderate degree of flat foot. The knee jerks were sluggish.

The urinary findings were normal; the blood count was normal and the blood Wassermann reaction was negative.

*Ophthalmologic examination* by Dr. Fleck revealed one-sixth normal vision with partial optic atrophy in both eyes, thickening of the vessel walls, and increase in the retinal pigment.

*Roentgenologic Examination:* The skull is abnormally large with flattening of the upper and posterior surfaces. The vertical diameter in the posterior portion is increased. All of the bones are of usual thickness and the sutures and grooves are normal. The sella is increased in depth and is somewhat closed-in. The frontal and paranasal sinuses are tremendously enlarged.

*Hands:* The bones are normal in appearance. Most of the epiphyses are fairly well united with the shafts, which is in marked contrast to those of her brother a year older, in whom they are widely separated.

*Feet:* The bones are normal in size and shape with the exception of the distal phalanges which are blunted at the tips.

#### DISCUSSION

In summarizing the results obtained by the study of these two cases, it is evident that the clinical manifestations are typical of the Laurence-Biedl Syndrome, the characteristic features being hypophyseal obesity, hypogenitalism, atypical retinitis pigmentosa, polydactylism and inhibition of mental development. Cases have been reported in which some of these cardinal symptoms were lacking—either the pigmentary degeneration of the retina or polydactylism.

There is considerable speculation as to the cause of this peculiar syndrome. No satisfactory explanation has been offered. Biedl does not think the disease is of true hypophyseal origin but of cerebral origin. Bardet believes it is due to a lesion affecting both lobes of the hypophysis during the period of embryonic or foetal development. Hydrocephalus has been suggested as a possible factor but few if any patients have presented direct evidences of the coexistence of this condition.

The syndrome bears a close resemblance to the congenital malformations occurring in achondroplasia, mongolian idiocy, dysostosis cleidocranialis and congenital club-foot, which Murk Jansen ascribes to increased amnion pressure due to an abnormally small amnion, the character of malformation depending upon the period of embryonic life during which the pressure was exerted. A lack of symmetry in the development of the toes is a feature in several of these conditions, as well as retardation of growth of the long bones of the extremities and alteration in the size and shape of the skull. Biedl emphasizes the structural changes in the sella as having some etiological significance.

#### THERAPY

In most of the cases reported no reference was made to the effects of organotherapy. However, Barnhardt reports two boys, aged 16 and 12 years, respectively, who were greatly benefited by the administration of thyroid, anterior pituitary lobe and calcium. The weight was reduced, basal metabolism was increased, and the muscles developed in both boys. In the older boy there was improvement of vision and genital development. They both became more active and attentive.

De Cyon observed a definite response to the administration of hypophyseal extract in a familial group of three boys. The headache disappeared. There was an improvement in their intellectual condition. The pulse became regular and slower, the weight decreased, and the height increased.

In one of Biedl's cases treated with thyroid and pituitary extract, the vision improved, menses were reestablished and the patient lost 13 pounds in weight. The brother of the patient also improved on the same treatment.

De Schweinitz also reports beneficial results in two of his three cases. He states that one of them responded well to organotherapy; vision, general condition and mentality showing distinct improvement. In the other case vision, which was rapidly declining, was maintained by pushing glandular feeding.

Bardet, Bartoletti and Solis-Cohen failed to get results with thyroid and pituitary feeding.

In my cases, the results of organotherapy, which consisted of thyroid and anterior pituitary lobe, have been very satisfactory, especially with respect to the improvement in the mental condition of the patient. As previously stated, the boy was 5 years in passing his first grade in school, and the girl, three years. They had just entered low second grade. Treatment was begun on October 8, 1927. On the fifteenth of October, the mother reported that both children were livelier and on the 22nd they began to take an interest in play and were less drowsy. The girl averaged 89 in her studies for the week. On November the fifth, the mother stated that both children were livelier than they had ever been before, and that Adolph made 100 in arithmetic and received three gold stars for correct papers. Isabella made 95 in arithmetic and 91 in spelling. On November 19th, Adolph's report showed 100 in four of his spelling tests and two gold stars, while Isabella made 100 in some of her tests. At the same time they became more active physically, their waddling gait improved, and they developed the habit of teasing each other. They both continued to improve mentally and physically until February 18, 1928, when they discontinued the treatment.

Their school reports at this time, for the previous week, showed that Adolph had three 100 marks in his studies and Isabella four 100 marks in her studies. Adolph had lost 18 pounds in weight. His circumference about the waist had decreased 3 inches and his genitals had markedly increased in size. Isabella had lost 17 pounds in weight and her circumference measurements also decreased.

Before treatment the mother had to put on their shoes and clothes, wash their faces, and comb their hair. They now began to take their own baths and dress themselves, and manifest an interest in their personal appearance, and a desire for new clothes. Their dispositions had entirely changed. Instead of being dull and apathetic they were bright, cheerful

and alert. They began to sing and whistle and engage in the usual school games.

Although they had no treatment for more than a year, they continued to improve. They both passed into high second grade in their mid-year examination and into low third grade in the Spring. Last month they passed into high third, where they are making good progress.

Clinically, they now present an entirely different picture. Their vision has improved, although they still show evidence of night blindness. They attend gymnasium regularly twice a week, read newspapers and story books, and play games. Adolph had to remain after school only once to complete his lessons; otherwise they required no special discipline in school. However, their mother still experiences some difficulty in managing them in their home.

Adolph weighs  $114\frac{1}{2}$  pounds and Isabella, 122 pounds. They have grown  $2\frac{1}{2}$  and 3 cm. in height, respectively. The skin over the lower extremities is much softer and less infiltrated although it is still abnormally thick. Adolph's gait is about normal, whereas Isabella still has some disturbance, especially in going up stairs. Isabella has a number of small, black pigmented spots on her face, neck and arms. These are peculiarly located in pairs from 0.5 to 2 cm. apart and vary in size from a pinhead to a small pea. In size, color and arrangement they closely resemble one of the original subjects of Addison's disease as reported by Addison himself. Whether the skin pigmentation has any relation to the pigmentary degeneration of the retina is doubtful. However, it suggests the possibility of a common etiological basis in which the suprarenal glands are involved. Adolph's genitalia have continued to develop but they have not attained normal size.

Psychological studies made by W. R. Casey of the Laboratory of Experimental Psychology, Johns Hopkins University, revealed some interesting facts as indicated in the following report and in the graphs.

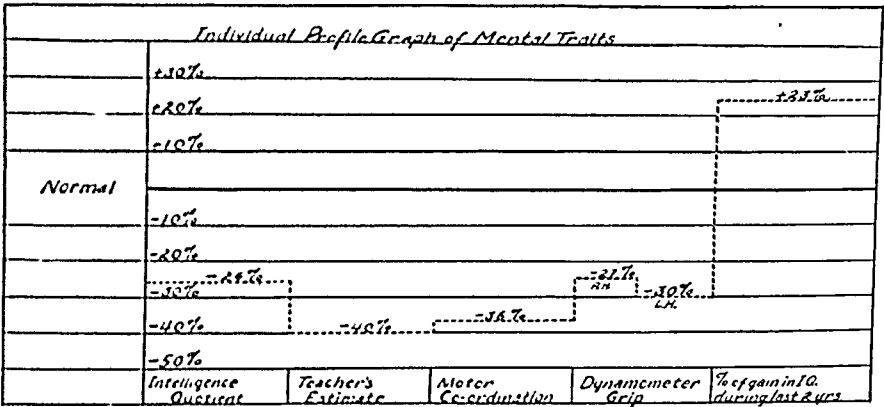
"Though limited to five or six ratings, the accompanying psychological profile graphs are interesting and significant in several details, and especially is this true when a closer study of the responses both subjects made in the Binet-Simon tests.

"First of all it should be said that mental tests involving vision, or tests which in any way tend to measure ability that ordinarily is acquired by previous visual experiences, should be interpreted with the handicap in mind which these two children work under. As far as possible in giving the Binet-Simon tests the alternates were used where otherwise vision might be a factor. On the other hand, it might be said that poor vision has been a factor in encouraging their auditory sense so that both of these subjects are especially alert in attending to what is said to them. This was shown by the exactness of their responses in repeating numbers and sentences read to them, even to giving the same inflection to the voice that the examiner used.

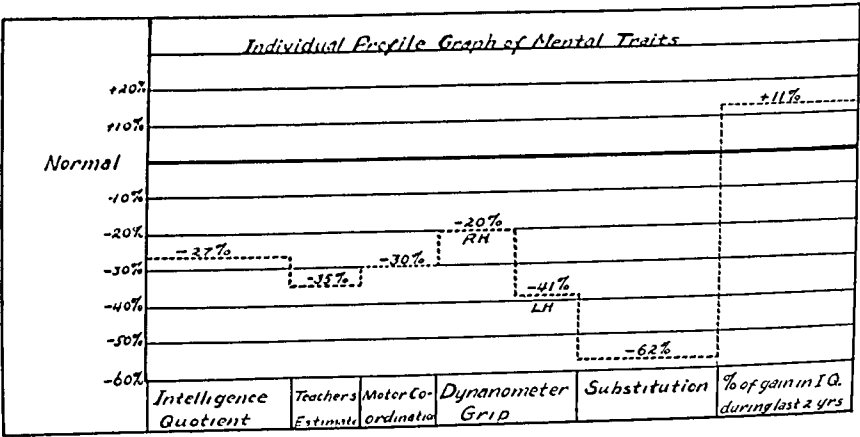
"Both subjects seemed to be able to attend easily to what was required of them. The boy is more alert and his reasoning ability better than his sister's, and had his vision been as good as hers he would no doubt have shown a much higher average on these tests, as well as a higher rating from his teacher. Taking all things into consideration, the native abilities of both children are much nearer normal than this psychological study shows, except in the matter of muscular co-ordination. They are both markedly below normal in this respect.

Perhaps the dynamometer and motor co-ordination results give a truer picture of their condition than any of the other ratings. The motor co-ordination test consisted of alternate tapping for the period of one minute.

“Without giving undue value to it, the percent of gain in Intelligence Quotient during the past two years should be considered significant. The original Intelligence Quotient, two years ago was determined by their teacher and a



*Adolph B*      *Age: 13 yrs 2 mos. Mental Age 9 yrs 10 mos.*  
*Tests given: March 21 1925, by WR Casey*



*Isabella B.*      *Age: 11 yrs 7 mos. Mental Age: 8 yrs 6 mos.*  
*Tests Given: March 21, 1929, by WR Casey*

liberal interpretation in their favor was made in compiling the ratings here given, and in spite of this, a very promising mental growth is indicated. What part of this growth in mental development is due to glandular therapy and what part is due to environmental changes, is impossible to say; however, the glandular factor no doubt has an important bearing and surely merits further study. It would be interesting and valuable to keep these two children on glandular therapy and test them from time to time to note further changes, especially in the matter of motor co-ordination.”

*Comment:* The object in reporting these two cases is to help to familiarize the profession with their nature. Doubtless many cases of this rare and peculiar disease exist which have not been recognized. Failure to diagnose may lead to blindness and imbecility in severely affected children. In the milder forms disability results from defective vision and mental deficiency. However, if the disease is recognized and proper treatment insti-

tuted, much can be done to arrest its progress and in some cases the vision, mentality, fat dystrophy and sexual infantilism can be improved by organo-therapy.

The tests used in making up the accompanying psychological profile graphs were:

1. The Stanford Revision of the Binet-Simon Tests
2. The rating listed on these graphs as "Teacher's Estimate" is made up of data furnished by their present teacher as to their class standing, number of children in their class, average age of these children, the standing of Adolph and Isabella relative to other members of their class as to comprehension of subject matter taught, ability to reason, ability to concentrate or focus attention, alertness, social adaptability in the school room, interest in their work, and ambition to succeed.
3. Motor coordination, or muscular control, was tested by the use of the Dunlap improved tapping plate. The score consisted of the total number of taps the subject made for a period of one minute divided into two parts, a half minute of tapping, then 15 seconds rest, and then another half minute of tapping. The graphs show the comparison of scores these two children made with that of norms established for their respective ages. An attempt was made to give them another motor control test, or what is known as Whipple's steadiness of motor control test, but their defective vision made this type of test unreliable.
4. The Smedley dynamometer was used in determining their strength of hand scores, and the graphs show their variation from the norms of children of their respective ages.
5. The Woodworth-Wells substitution test was given to Isabella only, as Adolph's vision was too poor for him to take it. This test might be interpreted as a learning test, and the low score which the girl made was greatly influenced by her poor vision.
6. The percent of gain in I.Q. as shown on the graphs is based on individual tests given them two years ago by their teacher and that obtained by the present examiner at this time, the results of which are shown by the first readings on these profiles.

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# A SUMMARY OF THE FINDINGS IN 1100 GLUCOSE TOLERANCE ESTIMATIONS\*

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I have attempted to analyze 1100 glucose tolerance estimations from the routine examinations at the Clinic during the past eight years. In order to get the information which this study offers into a brief concrete form so that one may have a general survey of the entire field, I have naturally had to sacrifice many interesting details and to group the individual curves into the series of twenty-three subdivisions which are given in Table I.

In this study I have devoted much time to the clinical investigation and interpretation of glycosuria, and therefore have studied this part of the general problem from the angles listed in Table I under the first five divisions. All the glucose tolerance curves were classified in the first place according to the patient's affections as given in Table I in the first column.

In the original classification the curves were considered as of four types: 1. Curves which presented a straight or almost straight line. 2. Curves which presented a moderate rise with a return to the normal level in less than two and one-half hours. 3. Curves which presented a more marked rise and return to the normal level in from two and one-half to three and one-half hours. 4. Curves which presented a high rise and a slow return, which, if projected, would extend over from four to nine hours. These four types of curves may be interpreted as follows: Type 1, strong tolerance for carbohydrates; type 2, normal tolerance; type 3, diminished tolerance (the potential diabetic, or the prediabetic as spoken of in the literature); type 4, the frankly diabetic curve.

In order to simplify the analysis further, I grouped types 1 and 2 as normal types and 3 and 4 as diabetic and the percentage estimation is based on this subdivision.

All tests were made while the patient was fasting. An ice-cold solution of 100 gm. of glucose in 250 cc. of water to which the juice of one lemon was added was given to the patient; an ice-cold solution is less nauseating than a tepid one. The blood sugar analysis was made and specimens of blood were taken just before and at intervals of one-half hour, 1 hour, 2, 3, and 4 hours after this administration and examined by the Meyer modification of the Lewis-Benedict method.

In an examination of the first three columns of Table I, under "Type of Curve," one can quickly discern the conditions which carry a high inci-

\*Read by title, Thirteenth Annual Meeting, Association for the Study of Internal Secretions, Portland, Ore., July 9, 1929.

TABLE I  
FINDINGS IN 1100 GLUCOSE TOLERANCE TESTS

The following findings..	Type of Curve			Renal Threshold			Blood Pressure			Relation of Fluid Intake to Output		
	Total Cases	Non-Diabetic %	Diabetic %	Total Cases	180 and Below %	Above 180 %	Total Cases	140 or Below %	Above 140 %	Total Cases	Output Less Than Intake %	Output More Than Intake %
All cases of glycosuria..	337	63	37	162	85.8	14.2	82	85.3	14.7	198	79.7	18.5
Glycosuria discovered during our examination.....	138	66	33									
Glycosuria discovered previous to our examination.....	199	60.3	39.6									
Glycosuria found in life insurance examination	61	62.2	37.7	54	89	11	17	94.1	5.8	61	88.2	11.2
Hyperglycemia found on routine examination..	65	60	40							62	93.4	6.4
Diabetic history in family (F. & H.)....	104	44.2	55.7	58	75.8	24.1	51	60.7	39.2	90	70.6	25.3
Obesity (46% male—54% female).....	172	31.3	65.6	100	54	46	120	57.5	42.5	114	80.5	18.6
Normal weight.....	287	74.2	25.8	31	83.8	16.2	62	80.6	19.4	283	82.8	16
Undernutrition.....	171	79	21	105	80	20	102	80	20	170	78.7	19.4
Hyperthyroidism (29% male—54% female)...	239	36.3	63.5	180	81.1	18.9	235	42.9	57.1	286	72.6	23.3
Hypothyroidism.....	9	89	11	5	100		8	100		9	77.7	22.2
Acromegaly.....	6	50	50	4	50	50	5	80	20	6	100	
Hypopituitarism.....	33	91	9	11	63.6	36.3	14	85.7	14.2	32	71.7	24.9
Hypertension.....	61	37.7	62.2	49	65.3	34.7	60	100		61	73.5	26
Pregnancy (Glycosuria)	21	57.1	42.8	17	94.1	5.9				21	81.1	14.2
Tuberculosis.....	8	62.5	37.5	6	66	34	6	100		8	62.5	12.5
Arthritis.....	17	52.9	47	9	55	45	10	100		17	88.3	11.8
Carcinoma.....	6	16.6	83.3	4	100		6	50	50	6	100	
Syphilis.....	17	41.1	58.8	14	71.5	28.5	11	81.8	18.1	17	82.5	17.7
Skin diseases.....	20	90	10	9	66.6	33.3	12	75	25	20	90	10
Patients under 20 years	77	70	29.9	33	63.6	36.3	30	86.6	13.3	77	78	22
Diabetes.....				54	27.7	72.2	33	66.6	33.3	335	78.2	17.1
Diabetic Symptoms— not diabetic.....				13	100		9	100		30	66.1	33

dence of diabetic curves, those giving an incidence of 40 per cent or more being the following:

Diabetic history in the family  
Obesity  
Hyperthyroidism  
Acromegaly  
Hypertension  
Pregnancy

Arthritis  
Carcinoma  
Syphilis

Thus in twenty-three subdivisions we find a heavy diabetic incidence in ten, or 43 per cent.

A similar examination of the columns under "Renal threshold" shows an incidence of a threshold above 180 in more than 30 per cent of the cases in which the following conditions were present:

Obesity  
Acromegaly  
Hypopituitarism  
Hypertension  
Tuberculosis  
Arthritis  
Skin Diseases  
Patients under 20 years of age  
Diabetes

It is hard to understand why young patients (patients under 20 years of age) should appear in this group, unless it be because in a large proportion of these patients hyperthyroidism was present so that we were dealing with a temporary physiologically high threshold. This, however, is contrary to my previous experience with cases of hyperthyroidism, as the threshold in this group at large is quite low. The diabetic patients gave the highest incidence of a high renal threshold, viz., 72.2 per cent. In Table II is given an analysis of renal thresholds according to decades, irrespective of any disease.

TABLE II  
RELATION OF THE RENAL THRESHOLD ACCORDING TO THE AGE  
(In Decades)

Decade	Total Cases	Average Renal Threshold
I	9	106
II	40	187
III	108	139
IV	201	141
V	242	155
VI	157	171
VII	76	148
Total.. .	833	149 Average

A similar analysis was made of the blood pressure in its relation to the blood sugar findings and the findings of this study are given in the columns under "Blood Pressure" in which the incidence of blood pressures above



and below 140 is given. An incidence of 20 per cent or more of blood pressures above 140 was found in the presence of the following conditions:

- Diabetic history in the family
- Obesity
- Undernutrition
- Hyperthyroidism
- Acromegaly
- Carcinoma
- Skin Diseases
- Diabetes

Finally, we analyzed the relation of water intake to urine output during the glucose tolerance test. Following the administration of glucose, there is at first water retention, the release of water occurring later on, toward the end of the test. If one ran the test five, six or seven hours, he would find this output to be increased in practically all cases. The conditions in the presence of which the output was more than the intake and in which the incidence of this increased excretion was 20 or more per cent, were as follows:

- Diabetic history in the family
- Hyperthyroidism
- Hypothyroidism
- Hypopituitarism
- Hypertension
- Patients under 20 years of age
- Diabetes

Briefly, we can draw the following conclusions from the above data: Patients with glycosuria are not all diabetics. About two-thirds are non-diabetic and one-third are diabetic, a finding which indicates the necessity of investigating each case carefully in order to determine its exact status.

When glycosuria occurs in the presence of pregnancy it is important to study the case carefully as the incidence of diabetes in this group is far above zero.

The discovery of glycosuria in the course of an examination for life insurance often leads to unfair discrimination. In my series as shown in Table I, 62.2 per cent of such cases were non-diabetic. These subjects are perfect life insurance risks.

The finding of hyperglycemia in the course of a routine examination ( $2\frac{1}{2}$  or more hours after a meal or during fasting), even though slight in degree, should not be disregarded, for in my series 40 per cent of such cases were diabetic.

When there is diabetic history in the family the diabetic incidence is higher than when such a history is absent.

Obesity, as is well known, carries a high incidence of diabetes, to say nothing of all the other evils which accompany this condition.

Normal or subnormal weight protects the individual against diabetes more than any other single factor. It means that the individual eats moderately, and moderate eating means that but a small load is thrown on the insulogenic function of the pancreas.

Glycosuria in the presence of hyperthyroidism carries with it a high incidence of diabetes, and for that reason should not be ignored, but the problems presented by such cases should be rigidly investigated.

Hypothyroidism is the reverse of hyperthyroidism and the incidence of diabetes among subjects of hypothyroidism is slight.

Acromegaly carries with it a high diabetic incidence.

Hypopituitarism carries with it a low incidence of diabetes.

Hypertension, on the other hand, as pointed out frequently in the literature, carries with it a high diabetic incidence.

Tuberculosis (glycosuria), arthritis, carcinoma and syphilis carry with them a high diabetic incidence.

Skin diseases carry with them low diabetic incidence.

Diabetes occurred in 29.9 per cent of patients under 20 years of age, these cases having been investigated because of their glycosuria.

# THE ABORTIVE ACTION OF LIQUOR FOLLICULI

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Following some clinic-therapeutic researches on the action of the "liquor folliculi" on animals, we had a chance of experimenting with this product on a cow, which had retained a dead fetus several months: the fetus could not be expelled by the usual means.

The liquor is prepared by one of us (Pighini) by drawing it with a sterile syringe directly from a cow ovary, centrifuging and phenolizing it at the rate of 0.80 per cent. Sealed in ampoules of 2 cc. it keeps sterile and active for a long time. Its activity measured in "rat units," according to Allen and Doisy's method of vaginal secretion as well as the activity of special preparations obtained from the original liquor, will be reported in another paper.

The same liquor was used on a Swiss cow, 6 years old, which, the owner stated, was 8 months pregnant, but which we found by rectal examination to have retained in the uterus a mummified fetus. After vainly trying the usual abortives—coitus, fatigue, massage of the uterus, warm irrigations, injections of barium chloride, and of yohimbin—we thought of trying to obtain an abortion by injection of freshly prepared follicular liquor. One cubic centimeter was injected hypodermically the first day and 2 cc. the second. On the morning of the third day the fetus was expelled. A few days later the cow was in rut and became pregnant. She later had a normal delivery.

The liquor of the ripe Graafian follicle, as known from the experiments of Frank (1922); Seaborn and Champy, Allen and Doisy (1923); Courrier (1924), etc., and from the more recent work of Laqueur, Brouha, Zondek, Massazza, Truffi (1927) contains in a high concentration a hormone which, injected in castrates or immature females, induces in the utero-vaginal tract the characteristic anatomo-physiological changes seen in the period of normal rut.

This hormone, which is contained in a very slight concentration in the corpus luteum (Frank and Gustavson); in the placenta (Iscovesco, Glim, Wadeln, Parker, etc.); in the blood (Frank, Goldberger); in the urine of the pregnant female (Zondek and Ascheim), is considered the natural metabolic product, which periodically stimulates the female genital functions, inducing those complex phenomena, which constitute the rut. The

histological modifications of the genital organs (uterus and vagina) induced through the treatment with this hormone are well known. They correspond exactly to the changes brought about by the physiological period of rut—hypertrophy of the uterus through proliferation of the muscularis, of the stroma and of the mucosa and glandular aspect of the epithelium; the vagina also shows stratification, cornification, exfoliation of the mucosa and its secretion—instead of leukocytes as normally—fails to show anucleated squamous epithelial cells as during the rut. The mammary gland also begins acinal proliferation.

What is of a greater interest in our case is the behavior of the uterus, which we saw to undergo remarkable hypertrophy under the action of the follicular liquor. Frank and his co-workers (1925) had already pointed out that the uterus of animals in rut, put into Locke's solution, shows rhythmic contractions ampler and slower than during the interoestral period or after castration. Brouha and Simonnet saw besides (1927) that these characteristic oestral contractions can be obtained in the uterus of animals in oestral rest by adding follicular liquor to the Locke's solution; and they showed, furthermore, that by steady washing the contractions fall, to reappear again following the addition of follicular liquor. In the washing water the active principles of this hormone are found, when the washed uterus no longer contracts rhythmically.

Following these experimental findings we applied our preparation of liquor folliculi to induce abortion. The result was prompt and there was no doubt but that it came through the action of the hormone.

A few cubic centimeters were sufficient to make the inert uterus of the cow pass into oestral activity, during which the muscular hypertrophy and the starting of the rhythmical contractions gave to the organ a reactive power sufficient to expel a *foreign body* kept there for months.

The applications of liquor folliculi in this field of the veterinary practice promise very much; and we intend to use such a method in the numerous cases of retention of the adnexae, as found very often in our province following infectious abortion.

#### SUMMARY

The authors have succeeded by the injection of a preparation of liquor folliculi in producing the expulsion of a retained fetus in the cow. The suggestion is offered that the method offers a possibility of wide usefulness in dealing with retained adnexae in veterinary medical practice.

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# PRELIMINARY NOTE ON THE ASSAY OF THE FOLLICULAR HORMONE BY VAGINAL ADMINISTRATION\*

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Previously it has not been demonstrated that it is possible to induce an artificial sexual cycle in spayed animals except by subcutaneous, intramuscular, or intraperitoneal injections of the ovarian "follicular" hormone. For practical purposes it would be highly advisable, in some cases, to administer this hormone by other routes and this study was instituted to determine whether or not absorption of the active principle could be obtained when administered by the vagina. Loewe, Laqueur and Hannan, have recently reported that oral administration of the estrus inducing hormone will induce the sex cycle in spayed animals in some cases but that the response is not certain, and the dosage required is very large. In the white rat it has been shown that as much as 100 times the subcutaneous dosage is necessary to induce estrus when administered orally. Evidently a large percentage is either destroyed in the digestive tract or is not absorbed across the intestinal mucosa.

As Macht has shown that the vagina has splendid absorptive powers in reference to many drugs it was decided to attempt the administration of the estrus hormone, by the insertion of gelatin pessaries in the vagina, in the various laboratory animals.

Glycerinated gelatin pessaries are made up by mixing 32 parts of gelatin with 48 parts of glycerin, heating with stirring until a homogenous mixture has been obtained and then 20 parts of extract are stirred in slowly. This solution was then sucked into small glass tubes and allowed to cool. After the gelatin had set the material was pulled out and cut into suitable lengths and dusted with talcum powder. The original extract of the follicular hormone contained 500 Allen-Doisy units per cc. Therefore each gram of pessary contains 100 units. The convenient size for use in a monkey was found to be anything from  $\frac{1}{4}$  to  $\frac{1}{2}$  gram.

## INJECTION OF AN EMULSION OF GELATIN PESSARY

In order to decide whether or not the hormone was destroyed in the process of making the pessary and further to determine whether the material had lost any stability due to this procedure an emulsion of the gelatin pessaries was prepared by dissolving a two gram pessary in 100 cc. of water and injecting it subcutaneously in spayed rats. The rat tests on all material were carried out according to the original Allen-Doisy technique giving 3 injections of  $\frac{1}{3}$  cc. each at 4 hour intervals. The results are

\*Read by title at the Thirteenth Annual Meeting of the Association for the Study of Internal Secretions, Portland, Ore., July 9, 1929.

given below in Table 1. The smears were indicated as follows: D—diestrus, OD—proestrus, O—estrus, and PO—postestrus. The rats weighed approximately 190 grams each. Usually five rats were placed on each dosage. Smears were taken approximately 48 and 56 hours after the first injection.

Table 1

Total Units Injected	Time of Smear	Vaginal Smears				
		1	2	3	4	5
2 U.	48 Hr.	OD	PO	O	O	
	56 "	PO	PO	PO	PO	
1 1/3 U.	48 "	O	O	PO	O	PO
	56 "	PO	PO	PO	PO	PO
1 U.	48 "	OD	O	PO	PO	O
	56 "	PO	PO	PO	PO	O

Apparently no loss of potency occurs in the process of making these pessaries. Further tests were made at varying intervals afterwards to determine the stability of the product. Up to the present time over a 4-month period no loss can be detected in these pessaries.

#### VAGINAL ADMINISTRATION OF THE OVARIAN HORMONE IN SPAYED RATS

Pessaries made according to the above formula contain 100 units per gram so that a piece weighing 10 milligrams contains one unit. By means of scissors pieces were cut and trimmed to weigh approximately 10 milligrams. This can be done with an error not exceeding 3 or 4 per cent. A group of rats weighing approximately 150 grams each were used. The pessaries were inserted in the vagina of the rat using forceps and a small plug of cotton inserted afterwards to keep the pessary in place. Two pessaries were administered to each rat at an interval of eight hours. Subsequently, smears were taken at 29, 46 and 51 hours after the first pessary had been administered. In no case did the animal show any response at the end of the 29-hour period. Table 2 shows the results obtained in a typical group of animals at the 46 and 51 hour periods.

Table 2

Total Units	Interval from 1st Pessary to Smear	Vaginal Smears				
		1	2	3	4	5
2	46 Hrs.	OD	OD	OD	OD	OD
	51 "	O	O	O	O	O
3	46 "	PO	O	O	PO	O
	51 "	PO	PO	O	PO	PO
4	46 "	D	D	OD	D	OD
	51 "	PO	PO	O	PO	O
6	46 "	D	D	D	D	
	51 "	D	PO	D	D	
8	46 "	O	O	OD	O	O
	51 "	PO	O	PO	O	O
12	46 "	PO	D	PO	D	D
	51 "	PO	PO	D	D	D

The smears taken from these animals showed a larger number of leukocytes than is customary. Probably the presence of a foreign body in the vagina had something to do with this. As will be noted from the above table, the response is less uniform than when the material is given by injection. However, this might be expected due to variations in the rat and the degree of absorption across the wall of the vagina. A fair response was obtained with two and three units, and results here given are inconclusive and demonstrates no exact ratio between the subcutaneous injection and the gelatin pessary dose. However, apparently it is in the neighborhood of three to one.

#### VAGINAL ADMINISTRATION OF THE OVARIAN HORMONE TO SPAYED MONKEYS

In a previous paper we have reported the induction of menstruation in spayed monkeys of the macacus rhesus species following the subcutaneous injection of the follicular hormone. It has been shown that menstruation always resulted if a sufficiently large quantity of the hormone is administered. The administration by the vaginal route was then attempted with the following results. Pessaries made as described above were inserted into the vagina by holding the lips apart with a small artery clamp while the pessary was inserted by means of a pair of small forceps. Sometimes, and especially so when large pessaries were used, it was found that the monkey succeeded in ejecting the pessary. This seldom occurred, however, when a pessary, weighing not more than  $\frac{1}{2}$  gram was used. In every case the administration of these pessaries was continued for six consecutive days, one pessary being given each day. About three or four days after the first pessary was administered the sexual skin started to redden and the labia and pouches to swell. The coloration reached a maximum toward the end of the administration of the pessaries and persisted for several days after the treatment had ceased. The swelling of the sexual skin decreased shortly after the color faded. Table 3 shows the results obtained in a small group

Table 3

Monkey No.	Weight	Date Spayed	Total Units Given	Color of Sexual Skin	No. Days Epithelial Growth	No. Days Menses	No. Days After Last Pessary that Menses Started	Date Pessaries Started	Remarks
1	3.6 kg.	4/30/28	600	1	9	4	9	3/11/29	
1	.....	.....	300	1	18	None	.....	4/ 1/29	
6	3.0 kg.	5/23/28	300	1	13	6	16	4/ 1/29	
7	2.3 kg.	5/23/28	600	2	9	6	12	4/ 1/29	
8	3.2 kg.	6/12/28	600	2	10	None	.....	4/ 1/29	
9	3.6 kg.	6/12/28	150	2	10	2	12	4/ 1/29	
10	2 1 kg.	6/12/28	150	2	10	6	11	4/ 1/29	
23	2 4 kg.	1/31/29	600	X	8	5	10	3/11/29	

of monkeys. Vaginal smears were taken daily and examined for signs of epithelial growth. The color of the sexual skin was rated as follows: X—pale, 1—faint red, 2—medium red, 3—red. The appearance of red blood cells in the vaginal smear was taken as the criteria of menstruation.

Failure in two cases to induce menstruation may be due to the fact that some of the pessaries may have been ejected and we can not be certain how many times this occurred.

#### SUMMARY

1. The estrus-inducing hormone was prepared in the form of a gelatin pessary for vaginal administration.

2. The check of potency of the gelatin pessaries by injection of water emulsion of these pessaries in white rats showed that no loss in potency occurred in their preparation.

3. The estrus cycle has been induced in spayed albino rats by vaginal administration of the follicular hormone. The ratio between the pessary dose and the subcutaneous dose is probably in the neighborhood of 3 to 1.

4. Menstruation has been induced in spayed monkeys by the vaginal administration of these pessaries. As low as 150 units will induce menstruation in these animals.

Further work is now in progress to attempt to establish accurately the ratio between the subcutaneous and vaginal dosage in both the rat and the monkey.



# Abstract Department

**The influence of tubercular toxin upon the suprarenals of albino rats.** Akiyama, S., *Folia Endocrinol. Japon.* 4: 22. 1928.

Tuberculin was injected subcutaneously into 34 rats over periods of ten or more days. No significant effect could be noted in the adrenal histology, weight or proportion between cortex and medulla. The thyroid similarly was unaffected.—R. G. H.

**Metabolism of rats after adrenalectomy (Metabolismo de las ratas suprarrenoprivas).** Artundo, A., Thesis for Doctorate in Biochem. and Pharmac., Nat. Univ. of Buenos Aires, pp. 1-86.—*Abst., Physiol. Absts.* 13: 1928.

Rats can survive extirpation of the suprarenals and show good nutrition and resistance to cold. They are, however, less active muscularly, fatigue more readily and are more sensitive to insulin and to avitaminosis B. Their muscles show increase of glutathione. The blood sugar is low for two to eight days after excision; the liver-glycogen is similarly low, but the muscle-glycogen is high. Blood sugar, liver-glycogen and muscle-glycogen all become normal in fourteen days after the operation. The animals are abnormally sensitive to the hypoglycemic and toxic action of insulin. Under a somewhat low external temperature (16° to 20°C.) the metabolism rises more and earlier than does that of the normal controls. But a severe fall of temperature (15° to 0°C.) raises the animal's metabolism less than in the normal controls. The results, like those of Cannon and his co-workers, and of Houssay, Lewis, Biasotti, and Molinelli, indicate that the suprarenals and adrenaline play an essential rôle in thermo-regulation.

**The effects of lowered temperature on adrenalectomized rats (La lucha contra el frío en las ratas suprarrenoprivas).** Artundo, A., *Rev. Soc. argent. de biol.* 3: 40. 1927.

Adrenalectomized rats show an inability to maintain a constant rectal temperature when placed in a cold environment showing a drop in body temperature of 15° as compared with an 8° drop in normal animals. Ability to compensate as determined by comparative death rates in cold environment increases with the time elapsing after the operation. Basal metabolism studied at 30°, 15°, and 0° shows that with a temperature drop from 30° to 0° the normal rat increases basal metabolism 2.45 times, while adrenalectomized rats increase but 1.86 times.—B. C.

**Influence of suprarenals on blood pressure regulation (Influencia de las glándulas suprarrenales sobre la regulación de la presión arterial).** Biasotti, A., Thesis, National University of Buenos Aires. P. 97. 1927.

The experiments were made on unanesthetized dogs, in order to avoid the perturbing effect of anesthetics. The blood pressure was taken on the femoral artery by the indirect method, precaution being taken to avoid emotional hypertension. Unilateral removal of the abdominal sympathetic chain, or extirpation of one adrenal was equally without effect upon the blood pressure. Removal of both adrenals caused a rapid lowering of the blood pressure until death. The removal of the right adrenal and the demedullation of the left was followed by a hypotension of 3-4 cms. Hg., which finally disappeared after 20 to 30 days.—J. J. Izquierdo.

**Some conditions affecting the capacity for prolonged muscular work.** Campos, F. A. de M., W. B. Cannon, H. Lundin and T. T. Walker, *Am. J. Physiol.* 87: 680. 1929.

By means of a treadmill, moving at a known speed and set at a known inclination, various conditions which might affect the maximal capacity of dogs to run were studied. With repetition of the tests the maximal ability increases.

The blood sugar as a rule decreases during the exercise period and rises slowly in the subsequent recovery period. No close relation was found between the glycemic level and the performance of the animal. Increase of the glucose percentage of the blood by preliminary injection of glucose and adrenalin has no favorable action on the performance. The lactic acid in the blood rises during the first stages of the work; then begins a decline which continues during the recovery period. No close relation was found between the percentage of lactic acid in the blood and the condition and performance of the animal. Preliminary injection of adrenalin may cause a rise of the lactic acid percentage higher than normal, but this is not associated with any definite effect on performance. A "large" dose of adrenalin (0.174 mgm. per kgm.) induces excitement and lessens the capacity to run. If animals run until exhausted and are then given subcutaneously "small" doses of adrenalin (0.02 mgm. per kgm.), they recover to a striking degree their ability to run. They may put forth energy from 17 to 44 per cent additional to what they have already put forth. Inactivation of the adrenal glands by removal of one and denervation of the other does not lessen the capacity for long-continued labor. The inactivation is associated with no marked influence on the glycemic level, but with a noteworthy reduction of the lactic acid rise during vigorous work. Severance of the sympathetic nerves of skeletal muscles does not reduce the maximal performance. Severance of the hepatic nerves results in a marked decrease of the capacity to run. Reasons are given for not attributing this result to the operation or to the effects on the heart rate. The capacity to run is largely restored by injection of adrenalin. Denervation of the heart, the adrenals and the liver is followed by a striking reduction in the ability to run. Injection of adrenalin then accelerates the heart and greatly increases the working capacity. The outstanding phenomena—the ineffectiveness of the glucose and lactic acid percentages of the blood, the favorable action of adrenalin, the unfavorable effect of hepatic denervation—are discussed in their bearings on the phenomena of exhaustion, but with questions suggested rather than answered.

—Authors' Summary.

Clinical studies of adrenalectomy and sympathectomy. Crile, G. W., *Ann. Surg.* 88: 470. 1928.

Adrenalectomy alone, or combined with sympathectomy, thyroidectomy, or with both, was performed in 29 cases in an attempt to control what the author calls the "kinetic drive" in certain diseases in which it is thought that the symptoms are or might be due to an increased output of adrenalin, or to the interaction of the adrenals and the thyroid gland. Experimental and clinical data support this theory in the case of hyperthyroidism, and although it is still too early to learn the end-results in these cases, the early results of adrenalectomy are very encouraging. The basal metabolic rate was reduced to normal, the thyroid gland diminished in size and grew firm in texture, and there was but little post-operative reaction. The results of the combined operations of adrenalectomy, thyroidectomy and sympathectomy in epilepsy are hopeful; the results of treatment in endarteritis obliterans and in hypertension are negligible, and those in neurasthenia inconclusive. The technique used in adrenalectomy is described.—Author's Abst.

Observations on the hemodynamic action of epinephrine. Dragstedt, C. A., *J. A. M. A.* 91: 1035. 1928.

The minimal effective dose of epinephrine on sustained administration in the unanesthetized dog produces pressor effects. The minimal effective dose of epinephrine in the unanesthetized dog is less than from 0.2 to 0.4 cc. of a 1 to 1 million solution of epinephrine per kgm. per minute. The vascular (pressor) response to epinephrine is more sensitive than the intestinal inhibition both in the unanesthetized dog and in man. The depressor response to epinephrine is an abnormal response mediated at least in part by anesthesia. Compatible suprarenal blood collected from one dog and injected into a second unanesthetized dog at the rate which it was collected has a slight pressor effect absent in the systemic blood. There is no reason to suppose from these experiments that the suprarenals are not normally and continually secreting epinephrine in amounts sufficient to modify the vascular bed, and there is reason to believe that an augmentation of secretion easily conceivable will have hemodynamic effects.—Author's Summary.

Further observations on adrenaline mydriasis at the menopause. Hannan, J. H., Brit. M. J. 2: 931. 1928.

Adrenaline mydriasis associated with the menopause in women has been shown to occur in 6 oöphorectomized rats. It was found to occur with more regularity in rats than in women. Large doses of the oestrous-producing autacoid caused rats to lose the adrenaline mydriasis effect. Doses corresponded to those necessary to produce oestrus. Diminution in the amount of the oestrus-producing hormone is responsible for adrenaline mydriasis at the menopause, and, as this phenomenon is always associated with severe vasomotor phenomena in women, is also probably responsible for these symptoms of the menopause. The oral administration of the oestrus-producing autacoid is rational treatment for the vasomotor symptoms of the menopause. The dose will have to be repeated within 7 days if a permanent effect is required. Though administration of the autacoid at the menopause is rational treatment, the enormous doses required will prevent the maximum benefit from such treatment being attained until preparations of increased activity are available.—R. G. H.

The hormone of the adrenal cortex. Hartman, F. A., K. A. Brownell, W. E. Hartman, G. A. Dean, and C. G. MacArthur, Am. J. Physiol. 86: 353. 1928.

Eight preparations of the adrenal cortex are described. The most potent extract is prepared by salting out the hormone with sodium chloride. The acetic acid filtrate of the cortex of ground ox adrenals is precipitated by saturating with sodium chloride and the precipitate washed with saturated sodium chloride solution to remove epinephrin. Separation and washing are carried out by means of a high speed centrifuge to reduce to a minimum the time of standing as a precipitate. The precipitate is then dissolved in water, the pH adjusted to 7.35 and the sodium chloride content to 0.9 per cent. One cubic centimeter of the finished extract is equivalent to 1 gram of cortex. Sterilization is accomplished by passing through a Seitz filter. Completely adrenalectomized cats injected twice daily with this substance have survived an average of 27.4 days or longer as compared to 5-6 days for controls. Cortin is proposed as a name for the hormone.—Authors' Abstract.

Observations upon adrenalectomized cats treated with the cortical hormone. Hartman, F. A., F. R. Griffith, Jr., and W. E. Hartman, Am. J. Physiol. 86: 360. 1928.

This is a study of adrenalectomized cats whose period of survival has been prolonged by injection of cortical extract. In many of these animals a condition of chronic adrenal insufficiency seems to have been produced. The symptoms were those of acute insufficiency except that they tend to develop more gradually. In six out of seven cats studied the metabolism remained within normal limits for periods ranging from 7-29 days after removal of the second adrenal. Adrenalectomized cats treated with extract never gained weight, although after it had dropped to a lower level it might be maintained there for some time. A lowered resistance to infection was common, many of the animals apparently dying earlier on account of some infection. Heat production and regulation were poor in treated adrenalectomized animals. Vigorous exercise, when undertaken, was always followed by unusual fatigue or depression. These adrenal insufficient animals were less able to take care of large quantities of protein or other food which might increase the demands on the kidney. Thus, eating of excessive quantities of beef or liver exacerbated the symptoms and sometimes caused death. The blood urea in these animals became very high. In a few instances the skin changed from pink to dirty grey in color. In one cat which survived 300 days a chocolate brown, subcutaneous fat was found. Thyroidectomy and gonadectomy did not modify the survival period of treated, adrenalectomized animals.—Authors' Abstract.

Adrenal secretion of a suprarenal gland anastomosed to the neck vessel, caused by stimulation of the splanchnic nerve or by nicotine (Descargos de adrenalina de una suprarrenal unida a los vasos del cuello, por influencia de la excitación del nervio esplácnico o de la nicotina). Houssay, B. A. and E. A. Molinelli, Rev. Soc. argent. de biol. 3: 509. 1927.

It is possible to effect vascular anastomosis of the suprarenal with the carotid artery and jugular vein of another dog. The gland thus anastomosed retains its vitality and its adrenal discharge increases when the great splanchnic

nerve is stimulated or nicotine injected. Stimulation of the great splanchnic nerve of the injected gland raises the arterial pressure definitely; this effect disappears after clamping the anastomosed vein and reappears when unclamping it.—E. A. Molinelli.

**Effect of neurine and ephedrine on adrenal secretion** (*Acción de la neurina y efedrina sobre la secreción de adrenalina*). Houssay, B. A. and E. A. Molinelli, *Rev. Soc. argent. de biol.* 3: 699. 1927.

The experiments were carried out on dogs with suprarenal-jugular anastomosis. Neurine, acting like nicotine, lobeline and quaternary ammoniums, produced great adrenal discharge. Under the effect of ephedrine, adrenin secretion occurred in 3 of 5 experiments. It was slight, in general, but sometimes prolonged. If the splanchnic nerves of the donor's gland were previously excised, neurine still produced increased adrenin secretion, but ephedrine failed to do so. It is concluded that adrenal secretion plays but a secondary rôle in the effects of ephedrine.—E. A. Molinelli.

**Pneumogastric nerves and adrenal secretion** (*Nervios neumogástricos y secreción de adrenalina*). Houssay, B. A. and E. A. Molinelli, *Rev. Soc. argent. biol.* 3: 563. 1927.

The experiments were carried on by the method of suprarenal-jugular vein anastomosis. A weak, faradic centripetal excitation produces a slight diminution, often followed by a slight increase, of adrenal secretion. Stronger electric stimulations of the vagus nerve or mechanical stimulations such as tying or sectioning produce a considerable reflex increase of adrenin output. Anesthesia or section of the previously cocainized vagus does not alter adrenal secretion, indicative that these nerves have no physiological, tonic, reflex or direct influence.—E. A. Molinelli.

**Dual calorigenic activity of suprarenal gland.** Koehler, A. E., *Proc. Soc. Exper. Biol. & Med.* 26: 296. 1929.

The author determined the calorigenic effect of epinephrin-free extracts of the suprarenal gland as one test of the potency of the extracts. Two suprarenal preparations of opposite calorigenic activity were obtained. One caused an increase of 70 per cent in the metabolism of a dog, and the other a decrease of 38 per cent. Single doses of the preparations were given orally. The effect on metabolism increased to a maximum and declined within 2 to 3 days.

—M. O. L.

**The effect of parathyroid medication on the action of adrenalin and on the content of the blood** (*Ueber die Einwirkung der Parathyreoideamedikation auf die probatorische Adrenalinreaktion und auf den Gehalt des Blutes an K und Ca*). Kylin, E., *Acta med. Scandinav.* 67: 287. 1927.

Having shown that calcium increases the effect of adrenalin in raising the blood-pressure, while potassium decreases it, the author investigated the effect of parathyroid medication on the adrenalin-reaction and on the K- and Ca-content of the blood. Patients in whom the adrenalin-reaction was vagotonic were given two parathyroid tablets three times a day. The Ca-content of the blood rose, the average rise being 1.45 mgm. per cent. The K-content of the blood fell, the fall ranging between 6.9 and 0.1 mgm. per cent. The K/Ca quotient was lowered, the average value being 2.50 before treatment and 2.12 after treatment. The effect of the medication upon the adrenalin-reaction was to render it less vagotonic, more sympathicotonic. After treatment, in three cases the reaction was sympathicotonic, in three it was normal, and in the other six it was less vagotonic than before treatment. The conclusion was drawn that the change in the K/Ca content of the blood and the change in the adrenalin-reaction brought about by parathyroid medication are in some way coördinated phenomena. In order to confirm these findings, simultaneous determinations of the adrenalin-reaction and of the K/Ca content of the blood were made in 153 cases, and, although there were many exceptions to the rule, it was found that in the majority of the cases a vagotonic reaction to adrenalin accompanied a high K/Ca quotient, while a sympathicotonic reaction accompanied a low K/Ca quotient.—E. P. McCullagh.

**Behavior of denervated spleen in adrenalectomized animal.** Lim, R. K. S. and H. C. Chang, *Proc. Soc. Exper. Biol. & Med.* **26**: 271. 1929.

The denervated spleen in adrenalectomized dogs was found to show definite contraction as a result of exercise, bleeding, CO and death. Administration of lactic acid, CO<sub>2</sub> and O<sub>2</sub> were without effect.—M. O. L.

**Adrenal function of the suprarenals on diphtheria intoxication (La función adrenalínica suprarrenal en la intoxicación diftérica).** Molinelli, E. A., *Rev. sud am. de endocrinol.* **9**: 902. 1926.

Rats are very sensitive to diphtheria toxin during the first 20 days after suprarenalectomy, but after 30 to 90 days they recover their previous resistance. Dogs without suprarenal medulla substance and with only the right suprarenal cortex are as sensitive to toxin as normal dogs. Diphtheria intoxication in dogs causes congestion of the gland but does not increase its weight. The quantity of adrenin content is frequently, but not always, diminished. The quantity of adrenin secreted, per kgm. per minute, is the same in poisoned dogs and in normal dogs. Stimulation of the great splanchnic nerve produces less adrenin output in poisoned dogs than in the controls. In dogs thoroughly poisoned by toxin, nicotine produces less adrenal hypersecretion than in normal dogs. The serious symptoms of diphtheric intoxication in dogs, asthenia, hypotension and vomiting cannot be ascribed to suprarenal insufficiency.

—Author's Abst.

**Vasomotor and adrenal-secretory reactions on dogs with diphtheric intoxication (Réactions vaso-motrices et adrénalino-sécrétices des chiens soumis à l-intoxication diphthérique).** Molinelli, E. A., *Compt. rend. Soc. de biol.* **97**: 1036. 1927.

Measurement was made of hypertension caused by stimulation of the splanchnic nerve or injection of adrenaline and then of nicotine before and after clamping the left suprarenal vein (the right suprarenal vein having been excised). In dogs poisoned with diphtheria toxin there is a marked diminution of the vasoconstrictor effect produced by the injection of adrenaline by stimulation of the great splanchnic nerve or by injection of nicotine. The left suprarenal vein being clamped, stimulation of the great splanchnic nerve and injection of nicotine produce much less hypertensory effect than in control dogs. There is, consequently, less vascular response to adrenaline, nicotine and sympathetic nerve stimulation and a diminution of adrenin output in diphtheria intoxication.—Author's Abst.

**Clinical contribution to the study of myasthenia (Contribution clinique à l'étude de la myasthénie).** Paulian, D. and C. Aricesco, *Presse méd.* **36**: 793. 1928.

The authors report three observations on myasthenia gravis. In two cases a very appreciable amelioration of symptoms was obtained by pluri-glandular opotherapy, but especially with suprarenal extract and strychnine. In the third case, the symptoms of myasthenia were accompanied by symptoms of Addison's disease, particularly the pigmentation. Suprarenal therapy was of no benefit and the patient died. The authors do not think that myasthenia gravis is caused by any suprarenal pathology.—R. C. Moehlig.

**Adrenal secretion in angiotomized dogs.** Popov, P., *Ber. ges. Physiol. exper. Pharmakol.* **44**: 86. 1928. Abst., *Chem. Absts.* **22**: 2970.

Blood drawn from the entrance of the lumbar vein into the inferior vena cava (London's technique) inhibits the contractions and lowers the tonus of the isolated small intestine of the rabbit. This stage is followed by an increased tonus and finally a return to normal. Blood from the femoral artery increases the tonus slightly and has no effect on the height of the contractions.

**The influence of the adrenal glands on resistance. III. Susceptibility to histamine as a test of adrenal deficiency.** Scott, W. J. M., *J. Exper. Med.* **47**: 185. 1928.

The resistance of rats to histamine was tested after double adrenalectomy and control operations. Of 12 rats possessing at least one functioning adrenal gland, all survived the intra-peritoneal or intramuscular injection of 10 to 20

mgm. of Ergamine acid phosphate. Of 36 doubly adrenalectomized rats, 34 were killed by this dose. This susceptibility to histamine is proposed as a functional test in studying deficient adrenal cortex function.—Author's Abst.

**Disappearance of adrenaline from circulating blood.** Sundberg, C. G., Upsala Läkaref. Förh. 33: 301. 1927. Abst., Chem. Absts. 22: 2970.

Adrenaline was infused continuously into the jugular and mesenteric inferior veins and into the femoral artery of cats whose spinal cords were severed between the 6th and 7th vertebrae. About 70-80% of the adrenaline was destroyed by the liver, 50% by the femoral capillary territory. Experiments with ligated hepatic vessels confirmed the important but not exclusive part of the liver in adrenaline destruction. Experiments in vivo did not confirm Tatum's statement that arterial tissue destroys adrenaline.

**Cress grown on adrenaline.** Thompson, J. H., Nature, Sept. 15, 1928.

A few experiments relating to the action of the internal secretions of animal glands upon vegetable life have yielded a somewhat extraordinary result with adrenaline. Cress seeds grown on pads of cotton well soaked in 1 in 10,000 solution of adrenaline showed the following marked differences from control crops grown on distilled water. There was a retardation in germination of approximately twenty-four hours. After the preliminary retardation, growth advanced at a rapid rate, and within three days the plants were considerably taller than the controls. When maturity of growth was reached the plants were much taller, and the leaves larger than the controls. Also, the plants were a paler shade of green. The most striking feature was the presence of adrenaline, or adrenaline-like compounds, in the "heads" of the cress. No adrenaline was added after the initial dose, and the wool pad was kept moist with distilled water. The plants were continuously exposed to the air and light. After carefully washing the cut "heads" of the plants they were reduced to a paste with distilled water, and the fluid filtered and tested for adrenaline. A deep rose pink color was obtained with the iodine test and other oxidizing tests for adrenaline. The control cress entirely failed to show any of these reactions. Some of the cress was extracted with normal saline and injected into decerebrate cats. Typical adrenaline curves were obtained, and it has been possible to demonstrate all the pharmacodynamical reactions of adrenaline in the cress.—Condensed.

**A function of the adrenal cortex.** Vincent, S., Nature, Dec. 29, 1928.

If both adrenal bodies be extirpated in a cat, the animal dies in three or four days. If the same operation be carried out in a decerebrate cat (brain removed to the level of the corpora quadrigemina), death ensues usually within half an hour. The fatal result is due to failure of respiration, and may be indefinitely postponed by artificial respiration. Close behind each adrenal is constantly found a lymph node, united to the cortex of the adrenal by a plexus of lymphatic vessels. If this plexus be torn across, or if the lymph node itself be removed, the animal will succumb with the same symptoms and within the same time as if both adrenal bodies had been removed. Further, if the lymph be prevented from reaching the blood-stream by tying both innominate veins, a similar series of events is noted. In several experiments, when the breathing had stopped for only a short time and the heart was still beating strongly, the respiratory function was temporarily restored by means of fresh watery extracts of the adrenal cortex. Destruction of the medulla of the glands produced no such results. Numerous controls of various kinds were carried out. Extirpation of the semilunar ganglia and section of all nerves in the region were without effect, so long as the arterial supply to the gland was not seriously interfered with. It was concluded that some substance, designated "pneumin," essential for respiration, is manufactured in the adrenal cortex and discharged into the circulation through the lymphatics. The conviction that the cortex and not the medulla of the gland is concerned is based upon the well-known fact that it is the cortex and not medulla that is essential for life, and that in the present series of experiments destruction of the medulla by cauterization produced none of the results described above.

—R. G. H.

The effect of adrenalin on the minute volume of the heart (*Die Wirkung des Adrenalins auf das Minutenvolumen des Herzens beim Menschen*). Von Euler, U and G. Liljestrand, *Skandin. Arch. f. Physiol.* 52: 243. 1927.

Adrenalin (.07 mgm.) was injected subcutaneously into a normal man in the nutritive and post-nutritive states. The effect of the drug in this dose is to increase the cardiac output per minute and per beat and to increase the oxygen consumption per minute. The oxygen consumption per liter of blood, on the other hand, is diminished, that is, the effect on the circulation is greater than the effect on the metabolism. The drug increases the heart-rate relatively more after a meal, hence the output per beat is increased less. The cardiac output was estimated by Krogh and Lindhard's nitrous oxide method. The work was performed by experienced workers and the conclusions drawn from 40 determinations are statistically valid.—W. F. Hamilton.

Innervation of glomus caroticum in man (*Die Nerven des Glomus caroticum beim Menschen mit kurzer Übersicht über den Histologischen Aufbau des Organs*). Riegele, L., *Ztschr. f. Anat. u. Entwicklungsgesch.* 86: 142. 1928.

A detailed description of the dense nerve plexus in and about the carotid body and the finer relations of the nerve fibers to the chromaffine cells. Ganglia cells of various sizes in small groups of 2 to 4 cells are described in the capsule as well as within the gland. Sensory nerve endings are also noted.

—A. T. R.

Diagnosis of pregnancy by detection of hormone of anterior lobe of hypophysis in the urine. II. Practical and theoretical results of urine investigation (*Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons*). Aschheim, S. and B. Zondek, *Klin. Wehnschr.* 7: 1453. 1928.

The authors have previously shown that hormones from the ovary and anterior lobe of the hypophysis are present in the urine not only at childbirth but also during pregnancy. Anterior lobe hormone is demonstrable as early as the fifth week after the last menstrual period, and ovarian hormone not until the eighth week of pregnancy. The technique is to inject a few cc. of urine from the patient into infantile mice, noting the effect on their ovaries, especially the formation of corpora lutea atretica and hemorrhagic follicles. During many thousands of injections into infantile mice, the authors have seen hemorrhagic follicles only when the injected urine contains the hormone from the anterior lobe of the hypophysis. The present report is based on the examination of the effect of the urine from 511 patients, and involves 2500 animals, which showed a mortality of 16-17%, certain urines being poisonous. The signs of pregnancy (corpus luteum atreticum and hemorrhagic follicles) in a control series of 258 cases (non-pregnant women and 15 men) occurred in only 4 cases, i. e., a failure of only 1.6%. In 197 normal pregnant subjects the signs appeared in all but 4 cases—a failure of only 2%. As little as .05 cc. of urine may give a positive test at the end of pregnancy. The reaction may disappear as early as 5 days after childbirth and regularly ceases 8 days after. Tubal pregnancy (14 cases) give variable results. Monkeys' urine acts like human. Anterior lobe hormone in urine of pregnant cows, pigs, mice, and rabbits was not demonstrable by this method.—A. T. R.

Studies in exhaustion due to lack of sleep. V. Effect on the thyroid and adrenal glands with special reference to mitochondria. Bast, T. H., J. S. Supernaw, B. Lieberman and J. Munro, *Am. J. Physiol.* 85: 135. 1928.

In the thyroid gland of rabbits exhausted through lack of sleep the following changes were noted: the number of mitochondria was markedly decreased; the nuclei were swollen and the decreased chromatin was clustered along the nuclear membrane. In the adrenal gland the following changes were noted: increased vacuolation of the cytoplasm with pyknotic nuclei; scattered patches of eosinophiles in the cortical sinuses; a marked congestion of the sinuses and vessels of the medulla with a colloid-like material and cellular debris; in the medullary-cortical zone the cells were large and had an embryonic appearance and between them degenerating cells were found.

—T. H. Bast.

**Sedimentation time in endocrinopathies** (*La eritrosedamentación en las endocrinopatías*). Bonilla, E. and A. Moya, *Arch. de med. chir. y espec.* **29**: 164. 1928.

From a review of the literature and a study of 35 clinical cases the authors come to the conclusion that the sedimentation time does not afford any useful criteria for the diagnosis of endocrinopathies.—R. G. H.

**The suprarenal and thyroid in relation to basal metabolism** (*Papel de la suprarenal y la tiroides sobre el metabolismo básico*). Demaria Massey, C., *Rev. Soc. argent. de biol.* **3**: 5. 1927.

Adrenalectomy reduces basal metabolism, as does also thyroidectomy in rats. When both operations are performed in the same animal, basal metabolism is lowered still further. The glands are independent in their action on metabolism.—B. C.

**Syndrome-Complex, Ménière.** Drury, D. W., *New England J. Med.* **200**: 173. 1929.

Of the six cases reported by Ménière, five were of the chronic type known as Ménière's symptom-complex, while the sixth was clearly a meningitis, an acute condition. On the acute case alone an autopsy was obtained, from which, illogically, the present conception of the disease is largely derived. Drury believes the underlying pathology of the syndrome to be labyrinthine irritation, and that attacks of labyrinthine vertigo are caused by increased or decreased intralabyrinthine pressure. An appreciable percentage of cases are of endocrine origin, and in the cases cited invariably are of the hypofunctional type. The severity of the symptoms varies with the nature and extent of the underlying lesion. It is emphasized that the symptom-complex may occur in patients suffering from deafness initially not of nerve origin, or the deafness may begin with the first labyrinthine attack.—Author's Abst.

**Rational endocrinology and organotherapy as foundations for greater efficiency in practice.** Sajous, C. E. de M., *Internat. Clin. (Series 38)*, **3**: 1. 1928.

Despite the considerable empiricism upon which organotherapy still largely depends, Sajous points out that endocrinology has nevertheless rendered valuable service in all directions, experimental as well as clinical. The erroneous and misleading view which unfortunately prevails to the effect that the functions of the ductless glands are unknown, frequently compromises life in acute cases and perpetuates suffering in many chronic disorders. The failure to identify the nature of the fundamental functions of the endocrine glands was due to a corresponding obscurity of various associated functions, particularly pulmonary and tissue respiration, heat production, metabolism, fever, hemolysis, autolysis, and the rôle of oxygen, lecithin and other lipoids and enzymes in the tissue cells.—I. B.

**Changes in hair following vasoligation.** Benjamin, H., *New York State J. Med.* **28**: 862. 1928.

Benjamin cites numerous cases from the experimental and clinical literature in which improvement in the growth and pigmentation of the hair followed ligation of the vas deferens. He cites a personal case in which this feature was noted.—R. G. H.

**On the female sexual hormone, menformone, especially on menformone as the hormone causing the growth of the mammae.** Borchardt, E., E. Dingemans, S. E. de Jongh and E. Laqueur, *Nederl. Tijdschr. Geneesk.* **72**: I. 2443. 1928. *Abst., Chem. Abst.* **22**: 4157.

Menformone injections in rabbits and guinea pigs (80 and 400 mice units, respectively, within 15 days) stimulate the growth of all sex organs. They also stimulate the growth of mammary glands in male guinea pigs and other animals. No other substance produces such actions. Menformone, present in the blood, is the cause of proliferation of the mammae, not only in adult women but also in newborn children. The internal parts of the mammary gland are over-developed under the influence of menformone. By continuous injections of menformone, the authors have been able to produce a regular abundant milk production from a male guinea pig.



**Bio-assay of preparations of ovarian follicular hormone.** Bugbee, E. P. and A. E. Simond, *J. Am. Pharm. A.* 17: 962. 1928.

The adoption of a standard technic for the bio-assay of preparations of the ovarian follicular hormone is proposed. The unit is that defined by Allen and Doisy as the quantity of material necessary to induce oestrus as judged by the smear method in an ovariectomized sexually mature rat weighing  $140 \pm 20$  grams. The technic is as follows: Select normal healthy female white rats between 3 and 11 months of age, keep them in well-ventilated, clean, dry quarters in which the temperature is maintained constant, between  $70^\circ$  and  $76^\circ\text{F}$ . Feed the rats an adequate amount of a well-balanced diet containing sufficient vitamins. Examine vaginal smears daily for a period of two weeks to determine if the oestrous cycles are regular. Perform complete double ovariectomy on those rats which have regular oestrous cycles at intervals of 4 to 6 days. If any doubt exists as to the completeness of the ovariectomy, take vaginal smears daily to make sure there are no spontaneous oestrous cycles. Prevent atrophy of the uteri by the injection of sufficient ovarian follicular hormone every week or every two weeks to cause oestrous growth of the uteri. After ovariectomy allow one week for recovery from the operation before making use of the rats for testing preparations. In testing oil solutions of the ovarian follicular hormone give 3 subcutaneous injections at 4-hour intervals in one day. In testing aqueous colloid solutions and true aqueous solutions give 8 subcutaneous injections, 4 on each of two successive days. Take vaginal smears at intervals of approximately 48, 52, 56, 72, 76 and 80 hours after the first injection. The reaction caused by the ovarian follicular hormone is the production of typical oestrus in which stage II of the vaginal smear contains only squamous cells. This reaction should occur in 48 to 52 hours after the first injection and should last several hours. Use at least 12 rats in testing a preparation, 3 to be given the same dosage. The minimal effective dosage is that in which 2 out of 3 rats given the same dosage show typical oestrus.—Authors' Summary.

**Treatment of menorrhagia of ovarian origin with insulin** (*Traitement des menorragies d'origine ovarienne par l'insuline*). Cotte, G., *Presse méd.* 36: 181. 1928.

The use of insulin to treat menorrhagia of ovarian origin followed the suggestion of Vogt of Tübingen. The author mentions having used insulin in forty cases of menorrhagia but only four case reports are given. It was assumed that the bleeding was of ovarian origin. There was loss of weight associated with the hemorrhages. Cessation of the bleeding was accompanied by gain in weight. Insulin is considered to have a selective action on the ovaries but the mechanism of this reaction is found difficult to explain. Theoretical possibilities for this specific reaction are discussed. The possibility that improvement of the general condition might be a factor in arresting the hemorrhage is not overlooked.—J. P. Pratt.

**Gaseous metabolism in a castrated man** (*Über das Verhalten des Gaswechsels bei einem Kastrierten*). Fischer, S., *Klin. Wchnschr.* 6: 2239. 1927.

The author studied oxygen consumption and carbon dioxide production on a castrated man over a period of about 14 months. There was a decrease in oxygen consumption following the removal of the second testicle. After the tenth day a gradual return of oxygen consumption to normal followed. There was a short period of increased carbon dioxide production which was followed by one of decreased carbon dioxide production.—R. Oslund.

**The male hormone.** Funk, C. and B. Harrow, *Proc. Soc. Exper. Biol. & Med.* 26: 325. 1929.

Using as a test of potency the increase in size of the comb in castrated cockerels, the authors believe they have demonstrated the presence of the "male hormone" in the urine of young men. The extract used was an evaporated filtrate obtained from an alcoholic precipitation. Castrated animals showed over a period of 7-12 weeks an increase in the size of the comb of about 30 per cent. Upon cessation of the injections the comb was reduced in size. Extracts of urine from men 70 to 80 years old caused a decrease in the size of the comb.—M. O. L.

Female sex hormones (Hormonas genitales femeninas). Garcia Triviño, F., *Med. Ibera.* 2: 225. 1927.

The author carried out a series of experimental investigations on the presence of ovarian hormones in the serum of pregnant women. It was found that the serum produces, in immature mice, a marked increase in the size of the uterus. The active substance is thermostable, soluble in alcohol and partly diffusible. The quantity present is about 10 units per cc. of serum. This reaction can be used for the diagnosis of pregnancy.—E. B.

Ovarian hormone in yeast (Weibliches Hormon in Hefe). Glimm, E. and F. Wadehn, *Biochem. Ztschr.* 107: 442. 1928.

Using an extraction procedure described in a previous paper, beer yeast and yeast cakes were examined for the presence of "feminin." The former gave 50 mouse units per kgm. of fresh yeast, the latter 30.—E. A. Doisy.

Effects of ovarian preparations on symptoms of the menopause and on basal metabolism. King, J. T. Jr., *J. A. M. A.* 91: 1423. 1928. *Abst., J. A. M. A.*

The effects of various ovarian preparations on symptoms of the menopause and on basal metabolism were studied. It was concluded that corpus luteum and whole ovary by mouth and follicular extract subcutaneously are probably useless for the relief of symptoms of the menopause. Bromide or phenobarbital or a combination of the two is distinctly helpful in the treatment of such symptoms probably not specifically but as mild general sedatives. Corpus luteum may raise a low metabolic rate in a patient at the menopause, but this effect is not sufficiently striking or constant to warrant definite conclusions. Fresh whole gland and follicular extract seemed to have no significant effect on basal metabolism.

A review of the work on the so-called rejuvenation process (Die historische Entwicklung der biologischen Alterbekämpfung). Klein, H., *Wien. klin. Wchnschr.* 41: 555. 1928.

The objective results reported by a number of workers have been: increase in weight, increase of erythrocytes, strengthening of muscles, decrease of high blood pressure, increased growth of hair and disappearance of cataracts, and, subjectively, increased vivacity, renewed physical and mental activity.

—L. L. Stanley.

Histological studies on corpora lutea, period of ovulation, relation between corpora lutea and cyclic changes in uterine mucous membrane, and the period of fertilization. Kyusaka, O., *Japan M. World*, 6: 147. 1928.

From observations in a large series of cases (Orientals), the author concludes that ovulation occurs from the 13th to the 17th day preceding menstruation. The period of possible conception he considers to be during the ovulation period and 3 days preceding it.—M. O. L.

Action of testicular injection on chronic ulcers of the legs (Acción del injerto testicular sobre las úlceras crónicas de las piernas). Maraño, G. and J. Ferrero. *Rev. Med. de Barcelona*, 8: 285. 1927.

The authors studied an adult with enormous ulcers of the legs and noted a condition of germoderma typical of testicular insufficiency. Following injection of testicular substance a rapid cicatrization of the ulcer occurred. This case, unique in the literature, shows the potential significance of glandular insufficiency in the genesis of chronic ulcers and points toward the desirability of a study of the endocrine condition in all such cases.—E. B.

Breakdown of the endocrine glands at the menopause and at puberty (Untersuchungen über Abbau von innersekretorisches Drüsen bei klimakterischen und Pubertätsblutungen mittels der Abderhaldenschen Reaktion). Melamed, L., *Fermentforsch.* 9: 306. 1928. *Abst., Physiol. Absts.* 13: 351.

An application of Abderhalden's reaction to determine the relation of the various endocrine glands to sexual function. At the menopause the blood shows a greater proteolytic activity towards ovarian and suprarenal tissue than at puberty.

**The present status of ovarian therapy.** Novak, E., J. A. M. A. 91: 607. 1928.

Great as have been the advances of the past few years on our knowledge of the physiology of reproduction, it cannot be said that they have as yet added very notably to the therapy of conditions dependent on disorders of ovarian function. The newer knowledge, however, offers a clear explanation of the failure of the ovarian therapy of past years, and, for the first time, justifies the hope that soon some of these functional disorders will be amenable to organotherapeutic measures. The question as to the singleness or duality of the ovarian secretion is still undecided, although the evidence indicates that the follicle and corpus luteum hormones are not the same, and that both play important parts in the human sex cycle. This factor, even more than that of inadequate dosage, is probably responsible for the unsatisfactory results achieved from the employment of the follicle hormone itself. For this reason, it is more logical to combine with it the use of corpus luteum extract, imitating the sequence believed to occur in the normal cycle. One of the problems still to be solved, in spite of the encouraging results achieved by individual workers, is that of preparing a potent corpus luteum extract. The standards of potency are very different from those of the follicle hormone. Both from a clinical and laboratory standpoint, the evidence indicates that the oral administration of ovarian, corpus luteum and ovarian residue extracts has little or no value in the treatment of such objective disorders as amenorrhea. In the treatment of the characteristic vasomotor symptoms of the menopause, there is much evidence, though necessarily only clinical, that oral therapy is of value. While the hypodermic administration of the newer extracts is the method to be preferred, it possesses serious practical disadvantages which will almost certainly limit its applicability. These disadvantages are enhanced for the present by the comparative scarcity of potent extracts and their rather considerable cost. As the ovarian follicle hormone possesses a slight effect when administered orally (not more than one-twentieth of the hypodermic effect) it is not impossible that some form of satisfactory oral therapy may be yet developed, either by developing new sources of supply or by increasing the potency of the substance by some artificial means. Recent investigations, which demonstrate the profound effect produced on ovarian function by repeated implantations of anterior pituitary gland tissue, lead to the hope that future work along this line may yield some method of applying this new knowledge therapeutically.

—Author's Summary.

**Source of the testicular hormone.** Oslund, R. M., Proc. Soc. Exper. Biol. & Med. 25: 845. 1928.

The growth and regression of combs of three capons was observed following injections (1) of extracts of pig epididymi and (2) of testicular fluid obtained from epididymus or the vas deferens. The results obtained point to the germinal elements as the source of the testicular hormone.

—Author's Abst.

**Rôle of the corpus luteum in maintenance of pregnancy.** Parkes, A. S., J. Physiol. 65: 341. 1928.

Technic is described whereby corpora lutea can be removed without eliminating ovarian endocrine function and with adequate control of operative shock, at the same time permitting proper experimental control. Mice were allowed to become pregnant after unilateral ovarian sterilization by x-ray. In all of 17 animals removal of the normal ovary with its luteal tissue resulted in termination of pregnancy within two days. In 8 mice removal of the sterile ovary alone did not affect pregnancy. Therefore, in this animal, corpora lutea of pregnancy are necessary until normal retrogression occurs, about the 17th day.—C. I. R.

**On the function of the prostate in relation to the basal metabolism—Experimental hyperprostatism (Ricerche sperimentali sulla funzione della prostata in rapporto al metabolismo basale—Iperprostatismo sperimentale).** Peracchia, G. C., Rev. sud-am. de endocrinol. 11: 311. 1928.

In 4 adult dogs prostatectomy caused a very slight increase in the basal metabolic rate. In 7 adult dogs after seven months' treatment with grafts of prostate glands from young dogs, and repeated injections of water-glycerin extract of prostate from young dogs the basal metabolic rate was decreased by approximately 25 per cent. The elimination of phenosulphonephthalein was

decreased about 20 per cent. The animals showed signs of precocious senility, as judged from changes in hair and skin. In 6 dogs receiving grafts or injection of extracts of prostate gland from old dogs, the same results were obtained, but in shorter time. In 4 senile dogs with hypertrophical prostate, grafts of testis or injection of water-glycerin extracts of testis from young dogs increased the metabolic rate about 25 per cent, increased the elimination of phenosulphonephthalein and reduced the size of the prostate. The author concludes that prostate gland grafts or extracts cause hypertrophy of the animals' own prostate and sclerotic changes in the testes.—G. V.

The action of the ovarian and the placental hormone in the pigeon. Riddle, O. and M. Tange, *Am. J. Physiol.* 87: 97. 1928.

The injection of the ovarian and placental hormone into immature doves does not hasten the attainment of sexual maturity in these animals. The idea that it does so in animals should be abandoned. Effects of subcutaneous injections of this hormone, during 3 to 7 days, on various organ weights were studied in 27 immature females (82 controls) and on 16 immature males (60 controls). In this part of the study the animals were killed for examination within 6 to 72 hours after the last injection. In both the ovaries and the testes of these birds growth was stopped, and an actual reduction in size usually occurred, as a result of this treatment. The oviducts of a few, but not all, of the treated birds showed the hyperplasia and hyperemia which characterize the action of this hormone. Weights of body, thyroids, suprarenals, liver, spleen, and bursa Fabricii were obtained in treated and control birds. The apparent changes in these organs are subject to qualifications fully described. The action of this hormone will remain imperfectly known until this has been studied on many organs other than the uterus and mammary of mammals. The true action of this hormone on the embryonic growth of certain organs in the mammal and bird can be tested properly only when the hormone has been obtained in a pure form. At present the hormone appears to be favorable for growth in accessory female genital organs only; it is adverse to growth in accessory male genitals, and to growth in the primary germ glands of both sexes.—Authors' Summary.

Quantitative histological methods in testicular investigations (*Zur Methodik der quantitativen histologischen Hodenuntersuchung*). Saller, S., *Ztschr. f. Anat. u. Entwicklungesch.* 86: 120. 1928.

A reply to the criticism offered by Schinz and Slotopolsky against Saller's results on quantitative determinations of the tubular and interstitial tissue of the testis by means of the planimeter. After comparing the relative accuracy of the cutting-out and weighing method with the planimeter, the author concludes that for all practical purposes the latter is sufficiently accurate.

—A. T. R.

Clinical and experimental contributions to the problem of testicular transplantation (*Klinische und experimentelle Beiträge zur Frage der Hodentransplantation*). Schönbauer, L. and F. Hogenauer, *Arch. f. klin. Chir.* 150: 333. 1928.

The Voronoff technic was used in making thirteen auto- and homo-transplants of testes in monkeys. Histological examinations of all these specimens showed that there was a necrosis in all of them which were transplanted from one monkey to another regardless of location. Some of the auto-transplants showed necrosis in the center but a few seminiferous tubules on the periphery where the blood supply was better. Transplanted testicles of the monkey were transplanted by Voronoff technic into four patients. The first showed a favorable result, the second showed no effect, the third one displayed more vigor after three months and a half, and the fourth showed, three months after the operation, an increased libido and more vigor. The authors conclude that, although the transplants did not live, a temporary clinical result was shown. This, they believe, was probably of a psychic nature.—L. L. Stanley.

A suggested test for pregnancy. Siddal, A. E., *J. A. M. A.* 91: 779. 1928.

One cubic centimeter of blood serum from patients was injected subcutaneously into immature mice daily for four or five days. On the sixth day the animals were killed and the ovaries weighed. The weight of the mouse was

divided by the combined weight of the ovaries, tubes and uterus, the resulting ratio being the criterion for a positive or negative reaction. Forty-five patients were tested. Twenty-five of twenty-six samples of serum from pregnant cases were positive. Eighteen of nineteen cases of non-pregnant subjects gave a negative response.—E. T. Engle.

**Macrogönitosmia praecox in a 4½-year-old boy with carcinoma of the third ventricle and an intact pineal gland** (*Makrogenitosomia praecox bei 4½ jährigem. Knaben mit Karzinom des dritten Hirnventrikels und intakter Zirbeldrüse*). Wieland, E., Schweiz. med. Wchnschr. 5: 114. 1928.

Wieland discussing *pubertas praecox* says that usually one of three glands are involved in tumor formation which produces the condition; the sex glands, the suprarenals or the pineal gland. The clinical picture is the same regardless of which gland is involved and the diagnosis is made usually by a process of exclusion. Wieland's case, diagnosed as a pineal tumor, was that of a previously healthy child of 4½ years. Six months previously the boy had developed headache, polyuria, polydipsia, emaciation, marked increase in height and a great increase in the size of the penis with long continued erections. The voice became deep, the testicles were the size of hazelnuts and hair developed on the pubis and upper lip. The penis was 10 cm. long when half erect. A growth in height of 11 cm. had taken place within a year. Radiograms of the hands, feet and skull were normal for his age. A Binét test gave an intelligence quotient equal to that of a normal child two years old. Symptoms of increased intracranial pressure developed, with convulsions and the patient died in coma. The autopsy revealed a normal pineal gland. The pituitary, cerebellum, pons, and aqueduct of Sylvius were normal. A tumor the size of a hen's egg was found in the third ventricle, spreading out into both lateral ventricles. The histologic diagnosis was carcinoma.—R. C. Moehlig.

**Influence of pituitary extract on water and salt excretion** (*Influence d'injections sous-cutaneées d'extrait hypophysaire sur la secretion renale d'eau et de sel marin*). Bijlsma, U. G., Arch. néerl. de physiol. 11: 413. 1926. Abst., Physiol. Absts. 13: 244.

One mgm. of standard posterior lobe powder injected into female dogs of 14 to 16 kgm. weight increased the NaCl output and concentration in the urine at once and the volume output in 2 hours; the maximum volume output occurred in the third hour when the NaCl output had fallen below the initial level. If 1 litre of water was given by mouth, pituitary extract postponed the diuresis for 3 hours, but the NaCl output (and concentration) were increased at once; if the animals were impoverished of chloride, much larger doses of pituitary were required to produce these effects—e. g., 2 mgm. instead of 0.08 mgm. If saline was given instead of water, pituitary extract had very much less effect in postponing the diuresis and increasing the NaCl output.

**The failures of Roentgen therapy in hypophyseal tumors.** Bourget, J., Ann. d'ocul. 8: 89. 1928. Abst., Arch. Physical Therapy, 9: 426.

In his 13 cases of hypophyseal tumors, the author tried roentgen therapy before operation in 9 patients with only temporary success or none at all. Cushing in his 258 operations saw only exceptionally a symptomatic improvement after roentgen irradiation, and never a real cure. Adson (80 operations) tried it with weak and strong roentgen doses and as a result has much more confidence in surgical treatment. Frazier (102 operations) considers the percentage of favorable roentgen results as very small, and Hirsch (more than 100 operations) has not had favorable results with roentgen therapy.

**The treatment of diabetes insipidus with pituitary posterior lobe extract applied intranasally.** Campbell, J. R. and H. L. Blumgart, Am. J. M. Sc. 176: 769. 1928.

Eight successively observed cases of diabetes insipidus of various etiologies have been studied. Intranasal application of posterior lobe pituitary extract was as efficacious as hypodermic injection in controlling the fluid intake and urinary output. Attention is drawn to the importance of inserting the cotton pledget soaked with pituitary extract high in the nasopharynx.—R. G. H.

**Treatment of diabetes insipidus by nasal doses of powdered pituitary lobe.**  
Choay, A. and Lucie Choay, *Presse méd.* 73: 1155. 1928.

The authors found that the polyuria in diabetes insipidus could be largely controlled by the application into the nostrils of a dried extract of the posterior pituitary lobe. The powder represents about 5 times the weight of the fresh gland. The patients take the powder as one takes snuff. They advise a therapeutic test by hypodermic administration of pituitrin in order to ascertain the response to posterior lobe treatment, before resorting to the nasal method. In patients with a polyuria ranging from 15 to 20 liters, the best results are obtained by administering from 15 to 20 centigrams a day divided into 3 or 4 doses. If the polyuria amounts to less than 10 liters, 5 to 10 centigrams suffice if administered in 2 or 3 doses during the day. In subjects whose polyuria exceeds 20 liters, a hypodermic injection of pituitary extract is given in addition to the nasal treatment. Obstruction or inflammatory diseases of the nasal passages impair the efficiency of treatment. If there are no rhinological conditions which would interfere this treatment should be offered to patients as well as the standard treatment.—Harvey G. Beck.

**Pituitary cachexia.** Frazier, C. H., *Arch. Neurol. & Psychiat.* 21: 1. 1929.

In a series of 216 cases of pituitary dysfunction only a single instance of advanced cachexia (Simmond's disease) was seen. This case is reported in some detail. The subject was a syphilitic boy of 15. The genitalia were underdeveloped and axillary and pubic hair was lacking. The thyroid was palpable. A roentgenogram showed a dense shadow 2.5 cm. in diameter immediately above the posterior clinoid process. This was diagnosed as a pharyngeal duct cyst. At operation the cyst was found to be partially calcified; it was mostly removed. Following this, marked mental retardation and partial blindness occurred. Occasional paroxysmal episodes followed by stupor were noted. Pituitary feeding was instituted and five months after operation marked improvement had occurred; the improvement began immediately after a severe bump on the head. The intelligence, which had become obscured previous to operation was regained. Death occurred 16 months after operation. The report concludes with an excellent discussion of hypophyseal cachexia.—R. G. H.

**Some properties of the separated active principles of the pituitary (posterior lobe).** Gaddum, J. H., *J. Physiol.* 65: 434. 1928.

An exhaustive physiological study of "oxytocin" and "vasopressin," confirming, in general, the work of other investigators, but showing that oxytocin has a depressor effect in the fowl and spinal cat. Vasopressin, besides its effects on blood pressure and diuresis, has a specific stimulant action on rabbit intestine and a dilator action on frog melanophores. The latter action is due to a third substance and it is concluded that vasopressin is not a pure preparation.—C. I. R.

**Interrelation of pituitary and thyroid in metamorphosis of neotenic Amphibians.**  
Ingram, W. R., *Proc. Soc. Exper. Biol. & Med.* 25: 730. 1928.

The anterior lobe of adult *Rana pipiens* was transplanted intraperitoneally into *Rana clamata* larvae of various stages of limb development up to a hind-limb length of 5 mm. Three transplants were made at weekly intervals into 35 tadpoles, allotted according to size into cultures of 5. Controls of approximately the same development were injected with bits of muscle. After the second transplant marked limb growth was noted; the general growth being accelerated to any extent only in the smaller tadpoles. After the twelfth day following the first transplantation marked metamorphosis signs appeared, and in from 25 to 33 days forelimbs began to push through and tail atrophy was observed. Most of the experimental animals were killed when they showed practically complete metamorphosis and the thyroids removed for examination. The control animals exhibited only slight normal growth and development and in no case showed any signs of metamorphosis. Pronounced development of the thyroids of the treated animals was found. Sections of the control glands displayed large, colloid-filled follicles with walls composed of flat, inactive-appearing cells. The thyroid of treated animals, on the other hand, showed considerable loss of colloid substance from the follicles with collapse of some of the latter, and extreme activity of the cells which were greatly elongated, with proportionate thickening of the follicle walls. Freeing of

colloid and heightened activity were evidently effects of the anterior lobe transplantations. The evidence would indicate that the neotenic condition in certain animals depends upon a defective relationship between the anterior lobe of the pituitary and the thyroid. Whether this depends upon a retarded anterior lobe development or upon a failure to release the anterior lobe active principle may be shown by subsequent experiments.—M. O. L.

**The mental disturbances associated with pituitary disorders.** Menninger, W. C., J. A. M. A. 91: 951. 1928.

From a study of 42 cases, it is concluded that there is no uniformity of association of any particular mental picture with any type of pituitary disorder. An unsatisfactory attempt to classify the mental reaction types under various pituitary groups disclosed: (1) a majority of cases of preadolescent hypopituitarism showing some degree of retardation in intellectual development; (2) a majority of postadolescent hypopituitary cases presenting the schizoid picture; (3) a predominance of the cyclothymic reaction in the late hyperpituitarism. Such observations cannot be assumed to prove the relationship between any specific type of dyspituitarism and any specific mental reaction type. However, there is an intimate association between mental disorder and dyspituitarism in (1) the concomitant development in children of pronounced pituitary disorder and mental retardation; (2) the concomitant onset and development of behavior disorders and the physical signs of dyspituitarism, and (3) the subsequent development of mental changes directly dependent on the physical signs of dyspituitarism.—Author's Summary.

**A case of eunuchoidism (Über einen Fall von Eunuchoidismus).** Munro, Ztschr. f. d. ges. anat. 14: 401. 1928.

This is a description with autopsy findings, anthropometric measurements and photographs of a 59-year-old man in which the testes showed atrophic tubules and a great increase in interstitial tissue, in which were many large circumscribed masses of epithelioid cells, resembling interstitial cells. In the hypophysis, next to the capsule, was a rim of adenomatous columnar cells. Basophiles are considered to be greatly increased.—A. T. R.

**Radiotherapy of tumors of pituitary.** Nemenow, M. and A. Udenburg, Strahlentherapie, 30: 239. 1928. Abst., J. A. M. A. 92: 1929.

In acromegaly the point of attack for the rays is the adenoma of the anterior lobe; the aim is to produce atrophy of the lobe and to lessen its secretion. In dystrophia adiposogenitalis success can be expected only if the cause is a tumor that compresses the pars intermedia, the posterior lobe and the chiasma. Results cannot be expected if the tumor proceeding from or exerting pressure on the posterior lobe is a cystic tumor, a structure that is but slightly sensitive to the rays. Certain tumors of the pituitary are extremely sensitive to irradiation, so that remarkable improvement follows a single treatment with radium or roentgen rays. Nemenow and Udenburg report on twenty-nine patients with pronounced roentgenologically demonstrable enlargement of the sella turcica and with endocrine symptoms. Eighteen (thirteen women, five men) had acromegaly, and eleven, dystrophia adiposogenitalis. In all of the patients with acromegaly except one, who had diabetes mellitus, the blood sugar was below normal, and all showed an increased tolerance of dextrose. The blood calcium was increased in all the cases. Treatment with radium and roentgen rays resulted in considerable improvement in all but one case. The severe headaches ceased entirely or were greatly lessened in intensity. Vision improved rapidly. The amenorrhea (eight cases) was not influenced, except for a temporary return of the function in three patients. In one of the latter, age 20, the infantile atrophic uterus attained normal size shortly after the treatment. In many cases there was marked improvement in the appearance. The blood calcium fell almost to normal. The ages of the eleven patients (seven men, four women) with dystrophia adiposogenitalis were between 20 and 50. The symptoms were of one to eleven years' standing. A marked change in the sella turcica was demonstrable in the roentgenogram in all. In eight, the walls were entirely destroyed and the floor was deepened. The destruction of the posterior portion of the sella and of the clivus blumenbachii explains the extensive disturbances of vision that were present. In one patient, age 21, in whom the disease began in childhood, the growth of the epiphyses

was retarded; the stage of ossification corresponded to the fourteenth or fifteenth year. Diabetes insipidus was present together with epileptoid attacks. There was high blood calcium, low blood sugar and increased tolerance for dextrose. In all except one of these patients there was great, sometimes startling, improvement after radiotherapy. The diabetes insipidus that was present in one patient disappeared. From this case and others observed by them, the authors believe that the pathogenesis of diabetes insipidus is to be explained by stimulation of certain centers from pressure by a tumor or from pressure on the infundibulum. To avoid recurrence, the roentgen treatment must be continued through a number of years with, of course, long intervals. In resistant cases it is combined with radium irradiation through the roof of the mouth. The article is illustrated by photographs, roentgenograms and diagrams representing the visual disturbances.

**The early clinical symptoms of disappearance of the anterior lobe of the pituitary (Simmonds' disease) (Die ersten klinischen Symptome bei Schwund des Hypophysenhinterlappens (Simmondsche Krankheit) und ihre erfolgreiche Behandlung).** Reye, Deutsche. med. Wchnschr. 54: 696. 1928.

Reye reports a case in a 35-year-old woman who, since the age of 20 years, had epileptic attacks which ceased after the birth of the first child. Following the second delivery, which was very difficult and attended by severe hemorrhage, requiring four weeks' stay in bed, she ceased menstruating, became very stout with a large pendulous abdomen and dry skin, was pale and became very sleepy. The basal metabolic rate was normal. From the clinical picture Reye diagnosed Simmonds' disease in the incipient stage. The patient was under observation in the hospital for five days. She received daily one ampoule of präphyson hypodermically and three tablets of the same preparation by mouth. The patient was much stronger five days after the treatment was begun, and had a return of sexual libido. Menstruation returned one month after treatment was begun and her weight decreased. Reye gives the symptomatology in the condition as follows: Difficult labor, severe hemorrhage, long convalescence, cessation of menstruation, loss of libido, increased fat deposit, increased bodily weakness and psychic disturbance. Paleness of the skin, falling out of hair and teeth, subnormal temperature, sense of coldness, digestive disturbances, eosinophilia, low blood pressure and cachexia. He says that gynecologists should have Simmonds' disease in mind when women do not menstruate for no known reason. He believes that the disease is caused by damage to the anterior lobe of the hypophysis following the termination of pregnancy.—R. C. Moehlig.

**Congenital and familial disease characterized by dystrophia adiposogenitalis with pigmented retina and polydactyl (Maladie congénitale et familiale caractérisée par une dystrophie adipo-génitale associée à une rétinite pigmentaire et à une polydactylie).** Ricaldoni and Isola, Presse méd. 36: 794. 1928.

Ricaldoni and Isola report observations on 4 brothers and sisters, the only survivors of 8 infants, the issue of consanguine parents. They were the victims of a singular malady characterized by dystrophia adiposogenitalis of the hypophysial type with pigmentation of the retina and polydactyl. The authors compare their cases with those of other authors (Bardet, Biedl) and insist on a familial syndrome in contrast to the purely accidental and the acquired type of Babinski-Fröhlich.—R. C. Moehlig.

**The role of the anterior pituitary in hastening sexual maturity in ring doves.** Riddle, O. and F. Flemion, Am. J. Physiol. 87: 110, 1928.

Anterior pituitaries of mature doves and cattle were studied as sources of a hormone capable of inducing gonad growth and precocious sexual maturity in immature doves. Tests were made on the effects of transplantation of 509 dove pituitaries, and of the injections of glycerin, acid and alcohol extracts of bovine glands. Daily homeotransplants produced increased growth in the testes of immature male doves. A less marked effect was found in some only of the ovaries. The intraperitoneal injection during 7 to 17 days of a glycerin (commercial) extract of fresh frozen bovine anterior lobes increased the testis size of 11 immature males by 50 to several hundred per cent. Similar dosage in 5 females probably produced a slight increase in the size of some of their ovaries. The acid and alcohol extracts of fresh bovine glands were without effect; but



the dosage may have been inadequate. Body weight was usually unaffected or adversely affected during the period of transplantation or injection. Birds receiving glycerin extracts usually had enlarged thyroids, livers, and spleens. Other treatments were probably without effect on organ weights. The work of others dealing with the anterior pituitary as the source of the hormone which accelerates the attainment of sexual maturity is confirmed, and is extended to birds. Earlier work of this laboratory has provided some evidence that in these ring doves the bursa Fabricii and the thymus retard gonad growth and sexual maturity. In the same animal the anterior pituitary is now identified as the source of a hormone which acts in the opposite direction. Here there is reason for regarding the actual time of sexual maturity as a resultant of these two forces.—Authors' Summary.

**Anterior lobe substance, the thyroid stimulator. IV. Effect in the absence of thyroid gland.** Schwartzbach, S. and E. Uhlenhuth, *Proc. Soc. Exper. Biol. & Med.* 26: 153. 1928.

Injection of preparations of anterior lobe of the pituitary had no effect on the metamorphosis of thyroidectomized axolotles. The authors believe that the anterior lobe is a specific thyroid stimulator, but that it can not replace the thyroid hormone.—M. O. L.

**Anterior lobe substance, the thyroid stimulator. I. Induces precocious metamorphosis.** Uhlenhuth, E. and S. Schwartzbach, *Proc. Soc. Exper. Biol. & Med.* 26: 149. 1928.

**Anterior lobe substance, the thyroid stimulator. II. Effect of feeding anterior lobe upon amphibian metamorphosis.** *Id.* 151.

**Anterior lobe substance, the thyroid stimulator. III. Effect of anterior lobe substance on thyroid gland.** *Id.* 152.

Intraperitoneal injection of anterior lobe substance and solution of dried anterior lobe powder into larvae of several species of Urodeles hastened metamorphosis. The authors believe that the action is through a stimulation of the thyroid gland.—M. O. L.

**Anthropometric investigations in acromegalics (Anthropometrische Untersuchungen an Akromegalen).** Westedt, A., *Ztschr. f. Konstit.* 14: 356. 1928.

Anthropometric measurements and photographs are given of a 45-year-old woman and a 56-year-old man with eosinophil adenoma of the hypophysis. Similar data are also recorded for a 27-year-old man with general features of acromegaly and giantism. These are compared with a case described by Ballmann and Hock and with normal proportions.—A. T. R.

**Acromegaly with unilateral paresis of 6th and 7th cranial nerves.** Wörster-Drought, C., *Proc. Roy. Soc. Med.* 21: 272. 1927.

The case described occurred in a man of 32 who complained of headache, dizziness, double vision, and facial paralysis. There were marked changes in the sella turcica which was greatly enlarged with indistinct margins. Although occasionally the 5th and 6th cranial nerves are involved in large pituitary tumors, this is not true of the 7th nerve. It is suggested that some hemorrhage had occurred from the presumably soft tumor, and that this involved the three nerves, including the 7th. The hemorrhage has become absorbed and the nerves are recovering.—I. B.

**Standardization of liver extract.** Beard, S. D., G. W. Clark, and M. J. Moses, *Proc. Soc. Exper. Biol. & Med.* 26: 13. 1928.

Rabbits injected intramarowly with *B. welchii* toxins rapidly become anemic and show many of the characteristic blood changes that occur in pernicious anemia in man. In 20 such animals given aqueous solution of liver extract by stomach tube, the results indicated a rough proportionality between the amount of liver extract given and the increase in the number of red cells and the hemoglobin content. This suggests the use of such experiments as a means of standardizing commercial liver extracts.—M. O. L.

Present results and outlook of diabetic treatment. Allen, F. M., *Ann. Int. Med.* 2: 203. 1928.

This paper is a review of the present knowledge of diabetes. In considering the diet of the diabetic the author never uses less than 60 grams of protein and usually 80 grams or more per day. The carbohydrate of the diet is always 50 grams or more, but the blood sugar is more easily controlled if the carbohydrate is limited. The fat intake should also be regulated. The most important factor is the total calories. The weighed diet is considered essential, but basal metabolism determinations are unnecessary because the number of calories needed is determined by the body weight and the amount of exercise. The calculation of the ketogenic-antiketogenic ratio is likewise unnecessary. The use of insulin should be avoided because of its inconvenience, but if the diabetes is severe enough so that dietary management leads to emaciation or disability, insulin should be used. The urine should be kept sugar free and the blood sugar normal. In the milder cases one injection usually at breakfast may suffice, but in the more severe cases the insulin may have to be divided into two or three doses. Insulin with proper diet should enable every diabetic to live out his normal life span, if there are no fatal complications. Coma or impending coma is best treated with large doses of insulin (200 units per 24 hrs.) and the administration of large quantities of fluid. Sodium bicarbonate in moderate doses (5-20 gm. total) is helpful. In impairment of circulation in arteriosclerosis, the feet should be observed frequently because of danger of gangrene. The best diet in the medical treatment of gangrene is one consisting of protein 50-80 gm., carbohydrate 80-120 gm., and fat to make 600-1200 calories. The diet should also be made salt free. Of the new diabetic remedies, synthalin will reduce the blood sugar, but it is somewhat toxic. Myrtilin has been of benefit experimentally in depancreatized dogs, but its clinical use has been unconvincing. Oral medication is one of the chief tendencies of modern diabetic research.—E. L.

The action of sulfur on carbohydrate metabolism (*Über die Wirkung des Schwefels auf den Kohlenhydratstoffwechsel*). Foldes, E., *Ztschr. f. d. ges. exper. Med.* 60: 571. 1927.

The addition of sulfur by means of skin inunctions was followed by a fall in blood sugar. The subsequent injection of adrenalin resulted in 5 of 6 experiments in a hyperglycemia. In one case there was a hypoglycemia followed by the death of the animal. Normal rabbits were given daily inunctions of sulfur for several months and then killed. Autopsy showed increased glycogen content of the liver, a hyperplasia of that organ and an increased sulfur content of the adrenals. The increased sulfur content of liver and adrenals was not found in the animal which died of hypoglycemia.—M. B. G.

Consideration of a typical case of pre-diabetes (*Consideraciones en un caso típico de prediabetes*). Garma, A., *Med. ibera*, 2: 190. 1927.

A man of 62 years with a familial history of diabetes presented an intense generalized stubborn pruritis. Injections of hypertonic glucose materially augmented the pruritis. The urine was normal but the hyperglycemia curve was very high. He improved very much on a regimen low in carbohydrates. Recently Schetz and Richter have advised injection of hypertonic glucose solution in the treatment of pruritis; beneficial results in such cases indicate the absence of diabetes, whereas an aggravating effect on the symptoms indicates disturbed carbohydrate metabolism. This case shows the necessity of preliminary determination of the condition of carbohydrate metabolism before instituting glucose treatment of pruritis.—E. B.

The effect of insulin on hypophysectomized dogs. Geiling, E. M. K., D. Campbell and Y. Ishikawa, *J. Pharmacol. & Exper. Therap.* 31: 247. 1927.

Completely hypophysectomized dogs, and also animals in which the "posterior lobe secretion" is absent or greatly diminished (as the result of cutting the stalk, inserting a clip around it, or interfering with the blood supply), are

hypersensitive to insulin. This hypersensitiveness increases as time goes on. At present in one dog weighing 7 kgm. marked "insulin shock" (hypoglycemia, salivation, prostration and convulsions) is produced by the injection of so small a dose as 1/7 clinical unit per kgm. of body weight. Several months ago it required a considerably larger amount to bring about a similar reaction. Normal dogs tolerate 2 and 3 clinical units per kgm. of body weight without any marked reaction. The authors put forward the suggestion that the increasing hypersensitivity of hypophysectomized dogs to insulin is perhaps explainable on the basis that the removal of the hypophysis leads to a degeneration of the thyroid gland, suprarenal glands and also the gonads. As is well known, these glands play an important role in carbohydrate metabolism. Removal of the anterior lobe alone does not make a dog more sensitive to insulin. Post-pituitary extracts injected into hypophysectomized dogs protect against insulin hypoglycemia and convulsions, while anterior lobe extracts do not afford such protection. There is also some evidence that smaller doses of posterior lobe extract may protect against insulin convulsions while not appreciably checking the hypoglycemia. The antagonistic action of the hypophysis to insulin is attributable to the hormone of the posterior lobe (including the pars intermedia) of the gland. Possible explanations for this antagonism are offered. Difference in sensitivity of animals towards insulin is probably partially due to varying degrees of pituitary activity, as well as to variations in thyroid activity (Burn and Marks).—Authors' Abst.

**Uses of glucose and insulin in diseases of children.** Gillespie, G. Y., South. M. J. 21: 834. 1928.

This combination can be used in certain cases of acidosis, recurrent vomiting, and acute intestinal intoxication. It is often remarkably effective.  
—J. C. D.

**The relative position of diabetes as a cause of death.** Hamblen, Angeline D. and E. P. Joslin, New England J. Med. 199: 933. 1928.

In Massachusetts, according to the mortality reports, in 1902 diabetes caused 0.8% of all deaths and in 1927, 1.7% of all deaths. This change is due to an actual increase in the number of diabetics, a reduced death rate from other causes, as well as changes in the classification of causes of death.  
—J. C. D.

**An insulin resistant case of diabetes.** Lawrence, R. D., Proc. Roy. Soc. Med. 21: 250. 1927.

This case occurred in a young diabetic man suffering with the severe form of the disease since 1925. Insulin failed to cause storage of glycogen, but did have its other action of checking the new formation of sugar and ketones from endogenous protein and fat. It seems probable that in this patient a factor other than insulin was lacking, perhaps some co-enzyme, which is necessary to the usual action of insulin in forming glycogen.—I. B.

**Adenoma of the islands of Langerhans with associated hypoglycemia.** McClenahan, W. U. and G. W. Norris, Am. J. M. Sc. 177: 93. 1929.

A case is reported in which periodic attacks of hyperglycemia were associated with loss of memory or consciousness in a patient who was found at autopsy to have a lesion of the island cells. The lesion consisted of a large circumscribed nodule (adenoma) which was found to be wholly composed of island cells. Islands in the remainder of the pancreas were found to be markedly hypertrophied. The significance of this relationship between hypoglycemia and hypertrophy or adenoma formation of the islands would seem to add further evidence toward the creation of a new disease entity.—

—Authors' Summary.

**An unusual type of insulin reaction in a diabetic patient.** Payne, W. W. and E. P. Poulton, Proc. Roy. Soc. Med. 21: 251. 1927.

This case occurred in a married woman of 46, who had suffered for four years with diabetes. Insulin produced such symptoms as headache, perspira-

tion, dizziness, and lack of control on walking. These were complained of for four hours after insulin injection. Meals relieved the symptoms, although the blood sugar continued to fall.—I. B.

**Respiratory metabolism of excised normal and diabetic tissue.** Richardson, H. B., R. O. Loebel and E. Shorr, *Proc. Soc. Exper. Biol. & Med.* 25: 658. 1928.

Studies were made of excised kidney and muscle tissue of normal and depancreatized dogs. The oxygen consumption of kidney and muscle was remarkably constant. The respiratory quotients of tissue from normal animals were within physiological limits and indicated that a mixture of food-stuffs was being oxidized. The respiratory quotients of isolated diabetic tissue were low and indicated that only a small amount of carbohydrate was oxidized. —M. O. L.

**Activation of insulin (Aktivering des Insulins).** Vogt, E., *Klin. Wchnschr.* 31: 1460. 1928.

By adding to insulin serum which is taken from women immediately preceding their menstrual periods the activity is markedly raised. At this time the serum contains the maximal amount of female sexual hormone. The same results are obtained if to the insulin the protein-free sexual hormone "Follikulin" is added. On the other hand, if we use serum taken after castration (operative or x-ray) one notes but a slight activation of the insulin. The raying of insulin directly (carcinoma dose) also causes a marked activation of insulin.—H. J. J.

**The direct stimulation of the islands of Langerhans by adrenin (Action stimulante directe de l'adrénaline sur les îlots de Langerhans).** Zunz, E. and J. LaBarre, *Compt. rend. Soc. de biol.* 98: 858. 1928.

The donor (dog) was decapsulated and the recipient depancreatized. Then the pancreatic circulation of the donor was connected with the carotid-jugular circulation of the recipient. Injection of adrenin chlorhydrate into the recipient resulted in a hypoglycemia.—J. C. D.

**Physiological variations in secretion of insulin (Contribution à l'étude des variations physiologiques de la sécrétion interne du pancréas).** La Barre, J. *Arch. intern. de physiol.* 29: 227. 1927. *Abst., Physiol. Absts.* 13. 1928.

1. Demonstration of a physiological insulinemia. If a depancreatized dog is transfused with a small amount of venous pancreatic blood the hyperglycemia is much reduced; normal carotid blood has hardly any effect. 2. The vagus as the insulin-secreting nerve. In cross-circulation experiments with dogs, stimulation of the peripheral end of the right vagus of the donor causes hypersecretion of insulin, as shown by the hypoglycemia produced in the receiving dog. The other effects seen in the receiving dog are the same as those occurring in a normal dog after injection of insulin. 3. Nervous regulation of physiological insulinemia. Cross-circulation experiments were carried out with dogs. One dog was rendered hyperglycemic by removal of the pancreas, and when it was transfused with blood from the pancreatic vein of the other dog, which had the vagi cut, there was no reduction of the hyperglycemia. This indicates that the normal physiological secretion of insulin is reduced considerably by interference with the nervous control through the vagi. Excitation of the vagus increases the antidiabetic effect of the pancreatic blood. 4. Hyperinsulinemia following hyperglycemia produced by dextrose injection. Using the same method, it was shown that intravenous injection of a large dose of dextrose increases the insulin content of the blood in the pancreatic vein; this increase is prevented by section of vagus or by atropine. Thus the higher nerve centers react to such a hyperglycemia by producing a compensatory hyperinsulinemia through the vagus. 5. Hyperinsulinemia following adrenaline injection. Intravenous injection of

adrenaline increases the insulin content of the blood in the pancreatic vein; as this increase is not prevented by section of vagus or atropine, it is not of vagal origin.

**Coagulation time in parathyroid tetany.** Brougher, J. C., *Am. J. Physiol.* **87**: 221. 1928.

In case of 18 dogs it was found that blood coagulation time was delayed in parathyroid tetany. Some dogs showed only a slight delay, while the blood of one in severe tetany did not clot for thirty hours. One ounce of cod liver oil or 0.4 cc. of acterol was efficacious in restoring normal coagulation time after a period of two to four hours in these animals with tetany. Animals receiving cod liver oil or acterol for twenty to forty days recovered, and in this recovery the blood coagulation and serum calcium returned to normal.—R. G. H.

**Treatment of parathyroid tetany with cod liver oil and yeast.** Brougher, J. C., *Northwest Med.* **27**: 329. 1928.

The post operative administration of cod liver oil and yeast to nine thyro-parathyroidectomized dogs delayed the onset of tetany and ameliorated its severity. The addition of a large amount of yeast to the diet did not prevent the anorexia. The animals kept on this diet for 30-40 days recovered and needed no further treatment. This same treatment in two patients increased the serum calcium to normal and relieved them of all symptoms of parathyroid deficiency. Two others who developed tetany during pregnancy were relieved of this condition by the use of cod liver oil alone. It would seem from these findings that tetania parathyreopriva is due to a deranged calcium metabolism which may be controlled by administration of cod liver oil and yeast.

—Author's Abst.

**Tissue changes in parathyroid tetany and in guanidine poisoning.** Elkourie, L. A. and E. Larson, *Am. J. Physiol.* **87**: 124. 1928.

In three dogs parathyroid tetany produced a marked congestion of the viscera. This congestion was not found in guanidine poisoning (6 cases—dogs, cats, rabbits). Necrosis was present in both conditions. Fatty degeneration of the liver was marked in guanidine poisoning, but absent in tetany. The symptomatologies of the two syndromes are quite dissimilar.—R. G. H.

**The influence of "Parathormone" on bone regeneration.** Fine, J. and S. Brown, *New England J. Med.* **198**: 932. 1928.

An attempt to determine the influence of Collip's parathyroid hormone (Lilly) on bone regeneration was made by hypodermic injections of the extract in a number of dogs on which subperiosteal rib resection was done. Four sets of young dogs were tested, one of each pair of the same age receiving the hormone. Regeneration was allowed to occur for periods varying from three to seven weeks in the different pairs. New bone formation was definitely better in the dogs not receiving the extract. But no essential difference was noted in two sets of adult dogs experimented with in the same way.—J. Fine.

**An intensive study of the thymus.** Bloom, J. C., *South. M. J.* **21**: 905. 1928.

This is a study of 107 children, varying in age from less than a month to six years, in whom there were thymic abnormalities. The author analyzes the symptoms shown and then gives typical cases. Two deaths, neither of them from enlarged thymus, occurred in the series. One treatment a week with x-rays was found safe and effective. Radium was unsatisfactory, as it was followed by anaemia.—J. C. D.

**Status thymicolymphaticus.** Hymanson, A., Arch. Pediat. 45: 592. 1928.

A four and half year old boy had always been well up to the time of report. Three days prior to admission he was taken sick with fever, rapid, grunting respirations and with a few scattered rales throughout the chest. X-ray examination revealed an enlarged thymus and peribronchial thickenings at bases of both lungs. The child died three days after admission. Autopsy findings showed broncho-pneumonia, rickets and status thymolympathicus. The thymus weighed 28 grams and extended to the base of the heart. The author feels that the broncho-pneumonia was too slight to cause death and that the enlarged thymus was the cause of death.—M. B. G.

**The diagnosis and treatment of enlarged thymus by x-ray.** O'Brien, F. W., New England J. Med. 100: 657. 1928.

Since there is no evidence that the thymus is not an integral causative factor in the type of death under discussion, and it is known that involution of the thymus takes place rapidly and without harm following x-ray or radium treatment, it would appear not only desirable but requisite, until such time as more exact knowledge or experience shall warrant a contrary opinion to prescribe radiation therapy for those children presenting x-ray evidence of "broadened mediastinal shadow" without symptoms in whom general anesthesia or surgery is contemplated.—J. C. D.

**The effect of synthetic thyroxin on the normal thyroid gland (Über die Wirkung des synthetischen Thyroxins beim Menschen mit normaler Schilddrüse).** Bauer, H. and G. Loewe, Deutsches Arch. f. klin. Med. 159: 275. 1928.

In a person with a normal thyroid, synthetic thyroxin is a hundred times as effective as dried thyroid substance. A single subcutaneous injection of 2 mgm. causes a rise in the basal metabolic rate of 10 to 30 per cent, which lasts from 24 to 48 hours. Daily repetition of this dose does not produce a corresponding increase in the metabolic rate. Following weeks of administration, intervals of rest can be introduced, since a considerable after effect is often maintained for two or three weeks. Without any alarming increase in the metabolism, the prolonged administration of large doses of synthetic thyroxin gives rise to toxic symptoms. Although thyrotoxicosis, with tachycardia, restlessness, tremor, sweating, loss of hair, anorexia, and diarrhea, can be produced by large doses of the thyroxin, to this substance can be ascribed a thyroid action that is not limited to oxidation changes. In normal persons, the dosage producing an increase in the basal metabolic rate is below the toxic dose. Without dietary supervision and restriction, efforts at weight reduction by thyroxin administration is without success because the increased appetite may result in the taking of such quantities of food as would maintain or even increase the former weight of the individual. An interesting observation with synthetic thyroxin was made in a case of nephrosis, in which, with the administration of this substance, the patient eliminated thirty liters of fluid.—I. B.

**Thyroid neoplasm with secondary deposits in skull.** Collier, J. S., Proc. Roy. Soc. Med. 21: 550. 1928.

The case described occurred in a male, 59 years old, who presented a swelling of the thyroid of 15 years' duration. This was painless, grew slowly but steadily. Five years ago the swelling had become so large as to occasion dyspnea and dysphagia. Operation was then performed and most of the thyroid gland removed, following which the patient improved and returned to work. Four years later he noticed a small lump on the skull, in the right parietal region. This had grown slowly and had become tender. The subject began again to have difficulty in swallowing and in breathing when he was lying flat. The skull presented a rounded hard mass in the right parietal region, which rose smoothly from the general skull surface.—I. B.

Statistics on Iodine-Basedow in Switzerland, between the years 1922 and 1924 (Die Schweizerische Basedowstatistik von 1922-1924). Flück, W., Schweiz. med. Wchnschr, 1: 2, 1928, and 2: 28, 1928.

This is a statistical discourse on the effect of iodized salt in goiter prophylaxis in Switzerland, as observed between the years 1922 and 1924, inclusive. Since opinions are divided on the value of this mode of goiter prevention, the Swiss health authorities at the request of the Swiss Goiter Commission, sent a questionnaire to all physicians requesting information relative to their experiences with iodized table salt. According to Flück, the minimal dosage of iodine capable of producing toxic symptoms is 0.5 to 1 mgm. Of the 457 Basedow cases reported by questionnaire, 182 were spontaneous hyperthyroid cases, 244 were iodine-Basedow cases, and 31 were of uncertain etiology. Of the spontaneous cases, 93 per cent were female and 7 per cent male. Of the iodine-Basedow cases 86 per cent were female and 14 per cent male. Though iodine-Basedow instances were frequently found in the young, the division of this condition into five-year stages shows, in males more than in females, an increase in iodine hypersensitiveness with increasing age of the individual. According to these statistics the minimal harmful dose of iodine was .7 to .85 mgm., and the minimal total dose was 6.8 mgm. In 39 cases in which iodized salt was used along with other iodine preparations, toxic symptoms developed when the salt was begun after a previously administered much larger dose of iodine was well tolerated. In several other cases iodized table salt could have contributed only a small part in the intoxication. In 25 cases ascribed to iodized salt solely, personal investigation revealed considerable uncertainty as to whether iodized salt was directly responsible for the toxicity. Since in America the iodine content of iodized salt is much greater than that of the salt used in Switzerland, the data pertaining to the result from the use of this prophylactic are by no means identical in both countries. The American dosage is not prophylactic but therapeutic and must lead to a disturbance in goiter districts. In Switzerland the daily dose of 1 mg. of iodine in previously existing Basedow's disease influences the symptoms at times favorably, at times unfavorably, while often no effects whatsoever are observed. Generally the harm outweighs the good. On the other hand, Swiss iodized table salt does not influence spontaneous Basedow's disease unfavorably. Since the advantages of goiter prophylaxis with iodized salt as employed in Switzerland are greater than the observed disadvantages the results of this investigation favor the adoption of this mode of goiter prevention.—I. B.

**Hypothyroidism with marked abdominal plethora and polycythemia (Insuficiencia tiroidea, pletora y policitemia).** García Morán, J. El Siglo Médico, 80: 223. 1927.

In a hypothyroid subject showing plethora and polycythemia, thyroid treatment resulted not only in marked improvement of other symptoms, but in reduction of the red cells from 6,120,000 to 3,090,000 per cc. This interesting result raised the question whether it should be ascribed to a specific effect of the medicament on the thyroid insufficiency as such, or an effect primarily on the plethora, which was diminished after the opotherapy. In view of all of the data in the literature on the effect of thyroid on the red cell count, García Morán inclines to think that the effect is an indirect one.—E. B.

**Differential diagnosis between hypothyroidism and hyposuprarenalism.** Koehler, A. E., J. A. M. A. 91: 1457. 1928. Abst., J. A. M. A.

The studies made suggest that much of the similarity and difference between hypothyroidism and suprarenalism lies in the possibility that in the former there is a primary depression of oxidation in the tissues, while in the latter there is a secondary depression due to faulty oxygenation, probably caused by vascular and muscular atonia, which in turn is caused by an impaired autonomic system due to cortical insufficiency. With these mechanisms as a background many bizarre clinical pictures may present themselves. The weakest structure or organ in the body is naturally the first to be affected by these glandular dysfunctions. Thus, a dry skin may for years be the only sign of

hypothyroidism, and later somnolence and fatigue may be developed, or vice versa. Similarly, hyposuprarenalism may first manifest itself as a marked depression of the higher centers, or as a severe low back pain, or as a gastrointestinal disturbance. Often patients are treated for these specific ailments, naturally without lasting improvement. The problem must always be to locate, if possible, the fundamental physiological disturbance of which these various ailments are only symptoms. To this end, accurate and careful diagnosis must precede treatment in the endocrine field.

**Studies in myxedema. VII. Another year of individual dosage treatment in thyroid therapy in childhood and juvenile hypothyroidism (Myxedem studien. VII. Ein weiteres Jahr individuell dosierter Schilddrüsenthherapie bei kindlichen und jugendlichen Hypothyreosen).** Kornfeld, W. and E. Nobel, *Ztschr. f. Kinderh.* 43: 65. 1927.

This is a report of additional investigation on the treatment of hypothyroidism on dosage based on the sitting height. Improvements are noted first in habitus delinquences (size of tongue, hair, skin), then in vegetative symptoms (obstipation), motor functions, growth and joint changes, length and mental development, in the chronological order named. The mental development does not hold pace with the physical improvement. Early treatment does not necessarily guarantee absolute improvement in mentality. The rapidity in ossification changes is a gauge of improvement.—M. B. G.

**Visceral projection reflexes in thyroid disease (Los reflejos de proyección visceral en la sintomatología de la glándula tiroides),** Maraño, G., J. Garma and A. Garma, *Med. iber.* 2: 205. 1927.

Sherrington and Mackenzie have shown that involvement of the viscera can lead to peripheral phenomena such as increased sensitivity of the skin and subcutaneous layer and muscle contractions (viscero-motor reflexes of Mackenzie), vasomotor phenomena, pilomotor phenomena, etc. Only recently have these reflex phenomena in thyroid disorders received attention. These local phenomena in the skin in the thyroid region can be designated in general "thyroid projection." In hyperthyroidism various signs of this sort have been described: hyperesthesia of the skin by Leon, marked reddening by Maraño and, recently, a number of regional vegetative reflexes by Serajski. After an ordinary dose of pilocarpin (about 1 cgm.) one observer reports in positive cases a reddening of the front of the neck and moderate or profuse local sweating. In the present paper are reported the results of a systematic investigation of these signs in fourteen patients in order to determine their relative frequency. It was found that none occurred constantly, that the most frequent was the marked erythema, that none of the projection phenomena were especially common in any of the clinical forms of hyperthyroidism, and that they were not quantitatively related with the clinical manifestations. These signs are chiefly of corroborative value. Only hyper-metabolism can be given unquestioned value in the diagnosis of hyperthyroidism.—E. B.

**Does the fetal thyroid gland function under normal physiological conditions (Gibt es eine unter physiologischen Verhältnissen erfolgende Tätigkeit der fetalen Schilddrüse)?** Maurer, E., *Ztschr. f. Kinderh.* 43: 162. 1927.

Based upon the amount of iodine found in fetuses and in adults, the author concludes that in intra-uterine life there is a fetal incretory function which parallels the maternal and which exercises its activity. Iodine is found in all the organs, but the largest amount is present in the thyroid. The literature on the subject is discussed. The consensus of opinion seems to be against the functional activity of the fetal thyroid.—M. B. G.

**Thyrotoxicosis from the internist's standpoint.** Miller, J. L., *Am. J. M. Sc.* 177: 98. 1929.

Our knowledge of the pathologic physiology of the thyrotoxicosis is extremely limited. In the present state of our knowledge, the term "thyrotoxicosis" is preferable to hyperthyroidism. "Thyrotoxicosis with nodular goiter"



is more accurate than "toxic adenoma." We are greatly in need of accurate information about the end results of subtotal thyroidectomy. Such information cannot be obtained by questionnaire. The patient must be carefully questioned and examined by a competent physician. As far as the writer has been able to determine, such a follow-up five years after operation has never been reported. The present method of treatment may be the best that can be developed. It cannot, however, be considered highly satisfactory.—Author's Summary.

**A carbohydrate diet for hyperthyroidism.** Moll, H., *Brit. M. J.* 2: 51. 1928.

Despite the diminished carbohydrate tolerance in subjects with Graves' disease, as evidenced by glycosuria and hypoglycemia, Moll urges the use of a carbohydrate rich diet in the management of these patients. In a study of 69 cases, it was found that as the general symptomatology improved through such a dietary, the carbohydrate tolerance likewise improved and urinary and blood sugar values became normal.—I. B.

**Changes in blood chemistry in animals with hyperthyroparathyroidism and in animals following thyroid feeding** (*Modifications de la constitution chimique du sang dans le syndrome hyperthyroparathyroïdien expérimental et chez les animaux simplement soumis au traitement thyroïdien*). Parhon, C. I. and Helene Derevici, *Compt. rend. Soc. de biol.* 99: 246. 1928.

Dogs were fed thyroid substance. The blood sugar, blood calcium and blood chlorides were increased, while blood urea and cholesterine were reduced in amount. The thyroid feeding was continued after thyroparathyroidectomy. The blood sugar showed a further increase; the blood calcium became normal or below normal; the blood cholesterine and urea were increased above normal; the blood chlorides were reduced below normal. Tetany is not directly dependent on the calcium content of the blood.—J. C. D.

**Synthetic thyroxin.** Sainton, P. and P. Vêran, *Paris méd.* 2: 48. 1928. *Abst., J. A. M. A.* 91: 839.

In their clinical studies Sainton and Vêran found that ingested synthetic thyroxin produces practically the same effects as thyroid extract. It can be given by mouth over a long period of time without inconvenience provided that small and progressive doses are used and that the patients are observed carefully. The authors found that in patients previously treated with thyroid extract 1.00 mgm. of synthetic thyroxin produces an action almost analogous to that produced by 0.20 gm. of the extract. They consider that in order to test the susceptibility of the subject, the initial dose of synthetic thyroxin in the adult should be 0.50 mgm. The progressive increase in the dosage must be carried out with caution and under strict surveillance of the patient.

**Thyroid-fed rats and high room temperatures.** Selle, R. M., *Science*, 68: 573 1928.

Repeated toxic doses of thyroid substance were found to render rats unable to withstand elevation of room temperature to 92° F.—R. G. H.

**Exophthalmic goiter. Report of two cases in children aged three and a half and six years.** Sherman, De W. H., *Am. J. Dis. Child.* 36: 636. 1928.

The author states that his case of exophthalmic goiter in a 3½-year-old girl is the 25th in the literature in children under 5 years of age. Another case in a 6-year-old girl is also reported. The first girl gave a history of thyroid dysfunction on the maternal side. Both the children showed an increased B. M. R. and hypertrophied tonsils. As the condition did not improve in either child, it was thought that removal of tonsils and adenoids would possibly be of material advantage. This was done in both instances, with improvement in the first child, but not in the second. As a preliminary operative care, compound solution of iodine, 5 drops three times a day, was given for two days in addition to intramuscular injections of 5 per cent solution of dextrose.—M. B. G.

The effect of thyroidectomy on skeletal muscle in sheep. Simpson, Ethel D., Quart. J. Exper. Physiol. 17: 31. 1927.

Sections of pectoralis major muscle from eleven cretin and five normal sheep were studied to determine whether or not there are changes in the fibers which would account for the condition of pot-belly and general weakness in the thyroidectomized animals. Normal cross-striation and all the structural features of voluntary muscle were clearly seen in the tissue from the cretins. In equal areas of longitudinal sections of the pectoralis major muscle there were fewer nuclei in the control than in the operated sheep. The removal of the thyroid gland resulted in a slower growth of cytoplasm and the nuclear-cytoplasmic ratio of the cretin remained more nearly like that of the young animal than that of the control. Comparison of cross-section area of fiber showed that in the operated lambs there was only slight increase in size during the first year (1.14), the muscle fibers showing considerable decrease in size in the five-year-old cretin. In the control the increase in cross-section was 3.82 times that of the eight-weeks' lamb, and a still further growth took place up to the fifth year. No consistent differences in nuclear structure were demonstrable in the normal and thyroidectomized animals. One may conclude that early thyroidectomy prevents the normal development of sarcoplasm, although no loss of striation or sign of degeneration of the muscle is evident.

—Author's Abst.

The relation of hyperthyroidism to benign tumors of the thyroid gland. Rein-hoff, W. F., Jr., and D. Lewis, Arch. Surg. 16: 79. 1928.

The authors studied 109 cases of nodular goiter and hyperthyroidism, reviewed 910 cases of hyperthyroidism, and studied 7 patients from whom sections of the thyroid gland were removed before, during, and after the administration of iodine. Before the administration of iodine, marked hypertrophy and hyperplasia were apparent in all cases. The glands could be divided into two groups. In one group the acini were normal in number, but increased in size and showed papillomatous infoldings, and in the other group they were small and more numerous, but without infoldings. These types were frequently mixed in the same gland, one type predominating. The remission induced by iodine was characterized by a change in the size and structure of the cells, a decrease in the polymorphous infiltration, and increased amounts of fibrous tissue. In this stage, certain areas did not fully participate in the regression, forming small areas of active parenchyma, whereas other areas went far beyond the average degree, forming the so-called involutinal bodies. The involutinal bodies fall into three groups. Those of the first group show a formation of large epithelium-lined cysts containing colloid; those of the second group, an encapsulated area of dilated colloid-containing acini; and those of the third group, actual disintegration of the parenchyma. Through pressure on the surrounding lobules and an increase in the stroma, these involutinal bodies suggest the appearance of encapsulated tumors, inaccurately termed fetal and cystic adenomata. The clinical improvement paralleled the extent of the involution. Cases in which there were spontaneous remissions and exacerbations showed nodules which were identical with the involutinary bodies except that they were larger. During an exacerbation, the epithelium underwent papillomatous infolding in the cystic and dilated acini. In the areas of hyperinvolution during an exacerbation, the peripheral acini were hypertrophied and hyperplastic. During a remission, these acini became more widely separated through further central disintegration of the body. These areas of hyperinvolution can be clinically detected as tumors, but do not represent true neoplasms.

The authors conclude that hyperthyroidism is invariably associated with hypertrophy and hyperplasia of the thyroid parenchyma. Nodules in these glands are due in the majority of cases to areas of regression which become encapsulated and enlarged as the disease process progresses. In a small percentage of cases the nodules represent areas of hypertrophy and hyperplasia in an otherwise normal thyroid, and in only a small minority of cases true benign adenomata. There is no proof that benign adenomata give rise to hyperthyroidism.—W. F. Rienhoff, Jr.

**Auto and homoiotransplantation of thyroid gland into brain of guinea pigs.** Siebert, W. J., *Proc. Soc. Exper. Biol. & Med.* 26: 236. 1928.

Guinea pig thyroid tissue was found to remain alive after homoiotransplantation into the brain for longer periods than when transplanted into the subcutaneous tissue. In the latter location the graft is killed chiefly through the activity of the host connective tissue and lymphocytes. The lymphocytic reaction is diminished in the brain, but that of the connective tissue is as pronounced as after transplantation into the subcutaneous tissue. Formation of new acini takes place to same extent in the homoiotransplant in the brain.

—M. O. L.

**Nodular goiter with hyperthyroidism.** Thomas, H. M., Jr., *Arch. Surg.* 16: 117. 1928.

Thomas analyzes thirty-two cases of nodular goiter associated with hyperthyroidism, but without the typical picture of exophthalmic goiter. He divides these cases into two groups, those of patients below, and those of patients above, forty-five years of age. Eleven of the thirteen younger patients showed typical hyperplasia and hypertrophy of the thyroid gland. One patient showed a small amount of hypertrophy and hyperplasia and presented clinically a doubtful picture of hyperthyroidism. Another patient showed a typical fetal adenoma, involution of the gland without hypertrophy and hyperplasia, and localized areas of hypertrophy and hyperplasia. In the nineteen patients more than forty-five years of age there was much less evidence of glandular hyperactivity, but on careful search, hypertrophy and hyperplasia were found in sections in every instance. Eleven of these patients suffered from heart disease. Of the ten patients who received iodine, three showed marked improvement, three showed slight improvement, two received no benefit, and two died.—W. F. Rienhoff, Jr.

**Hypothyroidism.** Warfield, L. M., *Ann. Int. Med.* 2: 446. 1928.

The author believes that more attention should be paid to the condition of hypothyroidism. The main symptom of which the patients complain is undue fatigability. Constipation is also common, due to the sluggishness of the bowels. Headaches and rheumatic pains were the chief complaint of a few. Patients may be either overweight, underweight or normal weight. There is no definite decrease in pulse rate and blood pressure. The basal metabolic rate in this series of 25 cases varied from minus twelve to minus thirty per cent. The author believes that a consistent minus 8 per cent in the B. M. R. may mean hypothyroidism. The condition can be corrected by the appropriate dosage of thyroid extract, 6-9 grains daily being the average dose.—E. L.

**Constitutional entity of exophthalmic goiter and so-called toxic adenoma.** Warthin, A. S., *Ann. Int. Med.* 2: 553. 1928. *Abst., J. A. M. A.* 92. 1929.

Warthin states that exophthalmic goiter, "toxic goiter," "hyperthyroidism" and "toxic adenoma" present always the pathologic picture of hyperplasia of the primitive lymph nodes of the thyroid, hyperplasia of the thymus and other anatomic stigmas of the thymicolymphatic constitution. In addition, they present certain constitutional peculiarities of their own kind. Not all cases of thymicolymphatic constitution will present the exophthalmic goiter syndrome, although all cases of the latter group will possess the chief morphologic stigmas of this constitution. All forms of exophthalmic goiter symptoms represent the abnormal reactions of a primary pathologic constitutional anomaly. Exophthalmic goiter, "toxic goiter" and "toxic adenoma" are pathologic reactions potentially predetermined in the individual at birth by virtue of his constitutional anomaly. The development of the symptoms, so far as the thyroid is concerned, is only the expression of the abnormal reactions of this constitutional anomaly to the conditions of the life of the individual. Only those possessing this constitutional anomaly will ever develop the so-called hyperthyroid or thyreotoxic symptoms. The potentiality may, however, remain "latent" or quiescent during the whole or a large part of the individual's life. The clinical and pathologic stigmas of the potential exophthalmic goiter constitution

may, however, be easily recognized in this individual. There can be no cure for the constitutional anomaly on which the development of "hyper" or "toxic" symptoms depend. These abnormal reactions may, and usually do, remain below the clinical horizon until called forth—in what way or by what mechanism is not yet fully understood. It is evident, however, that the thyroid gland is not the chief pathogenic factor in the various clinical syndromes usually referred to this organ; it is only an incidental complication or sequela, comparable to the participation in abnormal reactions of other organs and systems dependent on the constitutional anomaly. The most important histologic criterion of exophthalmic goiter, and of the allied clinical conditions of toxic adenoma and hyperthyroidism, as far as the thyroid itself is concerned, is the presence throughout this gland of hyperplastic primitive lymph nodes with germinal centers showing lymphoid exhaustion. Their presence determines the existence of the underlying constitutional anomaly. This potential exophthalmic goiter constitution may be recognized in the thyroid of very young children. To this constitution Warthin has preferred to apply the term "Graves' constitution." It is the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter and toxic adenoma.

**Hyperthyroidism in a 7-year-old girl.** Winograd, A., *Am. J. Dis. Child.* 36: 414. 1928.

The author reported a case of hyperthyroidism in a 7-year-old girl who presented tachycardia, pulse of 120, tremor, enlarged thyroid, basal metabolic rate of +6 and +27, and a cholesterol content of 168 mgm. per 100 cc. Hyper-trophied and cryptic tonsils and a sinusitis were considered as possible sources of infection.—M. B. G.

# ENDOCRINOLOGY

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## A FURTHER AND FINAL REPORT ON A CASE OF TETANIA PARATHYREOPRIVA, TREATED FOR A YEAR WITH PARATHYROID EXTRACT (COLLIP), WITH EVENTUAL DEATH AND AUTOPSY\*

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### INTRODUCTION

Late in 1924, J. B. Collip announced "the extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium." In a series of articles (1, 2, 3, 4), culminating in his Harvey Lecture (5) Collip presented convincing evidence of the potency of the extract. Suffice it to state that a stable and purified principle was obtained which, when injected subcutaneously into experimental animals, produced a rise in the blood serum calcium level, and which in overdosage resulted in an alarming and sometimes fatal hypercalcemia. It was furthermore shown that frequently repeated small doses of this extract are cumulative in action and will eventually raise the blood calcium to dangerous levels (values over 15 mgm.), due to a "pyramiding of the effect of each successive injection upon the preceding one." Hence the importance of accurate and dependable blood calcium determinations to control the dosage, very much as one checks the administration of insulin by blood sugar estimations, and watches the effect of thyroid extract by determinations of the basal metabolic rate. For the experimental proof, and also for an admirable review of the subject of tetany, the reader is referred to the articles alluded to above.

Soon thereafter reports began to appear of the clinical use of this new extract. Collip and Leitch (6) (January, 1925) reported the first case, namely, one of infantile tetany in a girl twenty-two months of age.

Crile (7) in the course of an article on "Surgery of the Glands of Internal Secretion," wrote as follows (July, 1925): "During the past six

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\*Read at the Thirteenth Annual Session of the Association for the Study of Internal Secretions, Portland, Oregon, July 5, 1929.

weeks we have been using the hormone discovered by Dr. J. B. Collip of Alberta University, and have secured as definite results as he secured with his experimental animals in both acute and chronic cases of tetany. Five acute cases have been treated with relief in every case; relief of symptoms is usually experienced within 20 minutes to one-half hour after the intravenous injection of one cc. of the hormone. In one exceedingly acute case, in which not a single one of the classical symptoms of tetany was lacking, the first dose was followed within twenty minutes by a disappearance of the subjective symptoms. Three doses of 2 cc. each resulted in complete recovery. Among the chronic cases treated relief has been secured in about 85 to 90 per cent." No detailed protocols were given and it is not known whether blood serum calcium determinations were made.

Davidson (8) (August, 1925) reports "a case of adolescent myxedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract." The patient, a girl aged seventeen years, was carefully observed from January 28, 1925, until her death, July 17, 1925. Exitus was attributed to a severe toxemia of undetermined origin. Post-mortem examination revealed a very small atrophic thyroid gland and no parathyroids in either upper or lower normal positions; two were found in median positions, the left one somewhat atrophied and the right apparently normal. A chart includes percentage of albumin in the urine, several blood cholesterol, blood urea and basal metabolism determinations, and a great many blood serum calcium determinations, together with the daily dose of parathyroid extract.

The authors (9) (September-October, 1925) reported the first detailed record of tetany in a human being resulting from accidental parathyroid extirpation (tetania parathyreopriva), in which Collip's parathyroid extract was used and controlled by blood serum calcium determinations. This paper covered the first five weeks of treatment; because of the favorable effects obtained it was thought advisable to publish immediately so that the medical profession might be informed of the clinical applications of this new hormone. This patient remained under continuous observation until her death, a period slightly over a year. It is this extended study, together with the vicissitudes encountered, the minute examination of the material removed at operation, and the findings at necropsy, which constitute the basis of the present contribution. The conclusions reached in our preliminary report and the data on which they were based will, for the sake of convenience, be referred to later when this patient's narrative is begun.

Shortly after our report (November, 1925) Snell (10) related the story of a woman, aged 54, on whom thyroidectomy had been performed for toxic adenoma, and who three years later (1924) was still suffering from tetany. At that time her blood serum calcium was 4.8 mgm. per 100 cc. Under massive doses of calcium lactate the patient improved, but the blood serum calcium could not be elevated above 6.7 mgm. per 100 cc. In April, 1925,

calcium lactate was discontinued and parathyroid extract (Collip) injected, a total of 5 to 10 cc. being given daily. A prompt rise in the blood serum calcium was noted, and although the average level tended to be higher than under calcium therapy, it again failed to reach a normal level. It was finally found that a normal blood serum calcium level could be maintained by the combined administration of calcium orally and parathyroid extract subcutaneously; the dosage required for this purpose was 14 grams of calcium lactate daily and one cc. of parathyroid extract (Collip) five times daily. Snell concluded: "That calcium lactate administered alone in maximal doses did not produce and maintain a normal level of blood calcium. The same is true of the dosage indicated for parathyroid extract alone. A combined treatment sufficed to attain and maintain a normal blood serum calcium level." The period covered by this latter treatment was about 26 days at the time of Snell's report.

In May, 1926, Hoag and Rivkin recorded the satisfactory effect of Collip's hormone in four cases of infantile tetany. Further reports of its use in this form of tetany have been contributed by Hoag, Rivkin, Weigle and Berliner (12), Sussmann (13), Leitch (14), and Gibson (15).

Lisser, Smith and Shepardson (16) obtained spectacular relief in a very severe case of tetania gravidarum by injections of this extract (the first injection was of 50 units, given intravenously, with relief of the most distressing symptoms within fifteen minutes).

Inasmuch as this paper concerns itself with the use of Collip's parathyroid extract in the treatment of tetany, no reference need be made to its use in sprue or Paget's disease (reports of which are to be found in the literature), or to the paper of Major and Buikstra, "The Effect of Parathyroid Extract and Liver Extract in the Hypertension Produced by Guanidine Compounds," nor to the paper of Cantarow, Coven and Gordon, "Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone," nor to the report by Mason of its use in chronic nephritis.

Monteith and Cameron (17) observed a patient for six months in whom tetany and hypothyroidism developed following a second thyroidectomy. The hypothyroidism was controlled adequately by desiccated thyroid. The tetany was partially controlled by calcium lactate orally and completely by injections of Collip's extract. Eighty-two days after operation the withdrawal of the extract resulted in the serum calcium falling to its initial low level, but some two months later on calcium lactate alone the blood serum calcium returned to normal. Subsequently, discontinuance of the calcium was followed neither by lowering of the calcium content of the serum nor by clinical symptoms of tetany.

By 1927 and 1928 sufficient time had elapsed since the introduction of Collip's Parathormone for clinical use, to enable several observers to report their experience in cases of parathyroid tetany where this preparation had been employed over periods of several months rather than a few weeks. As

might be expected, results varied according to the severity of the case. Noehren (18), for instance, in a case of tetania parathyreopriva obtained satisfactory results from relatively small doses of Parathormone (20 units daily, and later 10 units daily), very much as we did in our preliminary report (9). After two months he was able to decrease the frequency of Parathormone injections, and after six months had elapsed  $\frac{1}{2}$  cc. every twelve days was sufficient to permit the patient (a nurse) to resume active duty.

Hunter (19) published a case of post-operative tetany, the article being accompanied by a good chart, covering a period of three months. He administered 10 units of Parathormone three times daily, increasing to 15 units t. i. d. After 150 units had been given the serum calcium rose to 16.6 mgm. per 100 cc. During this same period thyroid substance was used (a point which will be referred to later in our paper). Results in this case were very satisfactory.

On the other hand, Hjort and Eder (20) report a case of adult tetany following thyroidectomy in which they encountered considerable difficulty with replacement therapy. Their patient was under daily observation for a period of three and one-half months. A calcium rich diet and rest proved unavailing. Large doses of calcium lactate (5 grams every four hours, day and night) were of some benefit, but under this treatment the fluctuations of the serum calcium were too great. Parathyroid extract given parenterally in large doses, 20 to 130 units daily, had little if any favorable influence on the condition. Parathyroid extract administered parenterally in doses of 130 units a day produced a satisfactory reaction in the serum calcium only when supplemented by oral thyroid therapy. Large doses orally, 3 grams daily, of dessicated parathyroid substance (166 times the ordinary dose), failed to influence the serum calcium, even though accompanied by thyroid therapy. They conclude that replacement therapy is not to be relied upon to too great an extent, and that preventive measures, such as autotransplantation of at least one parathyroid gland, may be more dependable. Other reports which might be cited are those of John (21) and Sahlgren (22).

Returning to our original publication in 1925 (9), the patient was a woman, 30 years old, who had been operated upon for a large adenomatous goiter; the mass extended under the sternum and posteriorly behind the trachea; the patient promptly developed tetania parathyreopriva. Thereupon a careful search was undertaken of the goitrous tissue removed, and three separate parathyroid glands were identified; the status of the customary fourth glandule was then unknown. This patient was treated with injections of Collip's parathyroid extract and a detailed account of this treatment, together with its effect on the blood serum calcium, was summarized in a chart and published in the article referred to above. During the first three weeks parathyroid extract alone was administered. We were struck by the fact that subjective improvement was almost immedi-



ately effected by the parathyroid extract, and preceded by several days the objective improvement, as evidenced by the reaction to Chvostek and Trousseau's manoeuvres, and that the relief of both subjective symptoms and objective signs occurred considerably in advance of any marked elevation of the blood calcium. Our report covered the first month of treatment, beginning immediately after the appearance of symptoms of tetany.

In summarizing this initial experience, we were led to the following comment: "It is perhaps premature at this writing to forecast the future of this patient, but it would seem likely that she can be kept free from symptoms and her blood serum calcium maintained at a normal level by the injection of small doses of parathyroid extract combined with calcium lactate by mouth.

"In view of the fact that at least three parathyroid glands were inadvertently removed, it is altogether probable that treatment will have to be continued more or less indefinitely. This is in accordance with the necessity for life-long administration of thyroid extract in pronounced myxedema. If this individual still possesses one parathyroid gland, compensatory hypertrophy may gradually ensue and eventually produce sufficient hormone to maintain a normal blood serum calcium. The authors hope to keep in touch with this patient and render a further report after long-continued observation."

This further report, long delayed, is herewith presented. Our patient was continuously under observation from the onset of symptoms, September 28, 1925, until her death, October 11, 1926. There are appended, for those who wish to study the story in detail, nine tables, which include the daily dosage of Parathormone and (when given) of calcium per os, as well as the blood serum calcium determinations\*; the daily dosage of thyroid substance per os (when given); and occasional notes of her clinical status. Throughout this year of treatment a chart was faithfully continued which graphically expressed the three significant factors, namely, the daily Parathormone dosage, the daily calcium dosage, and their effect on the blood serum calcium level. These three factors formed curves which ultimately extended over about 20 feet of graphic chart paper. It was found impossible to reduce this interesting graph to a size suitable for reproduction without rendering it illegible. Significant portions of the chart, however, have been selected for publication and will be referred to later.

To facilitate narration, the year's story of treatment has been divided into eight chapters.

#### CHAPTER I. (*September 28th to October 12th, 1925.*)

This period covers the first two weeks following the onset of tetany. During this time therapy was restricted to daily injections of parathyroid extract which varied from 0 to 37.5 units per day (see Chart No. 1). It

\*The blood serum calcium was estimated by the Collip modification of the Kramer-Tisdall method.

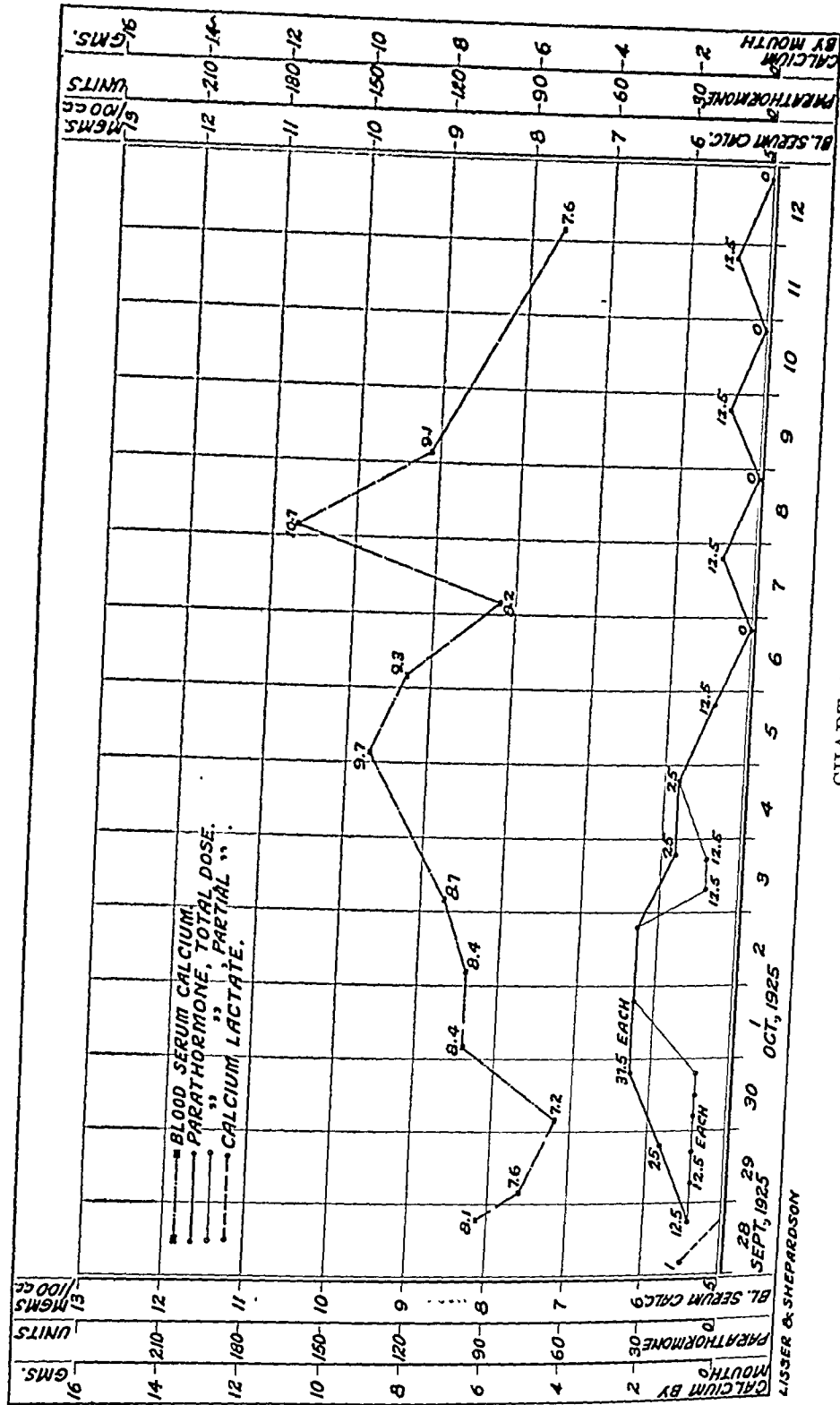


CHART 1

LISSE & SHEPARDSON

will be noticed that these relatively small doses of Parathormone succeeded in raising the blood serum calcium from 7.2 mgm. per 100 cc. on September 30th, to 9.7 mgm. on October 5th. Fearing a cumulative action from further administration of this potent parathyroid extract, no injection was given on October 6th and only 12.5 units on October 7th. The following day the serum calcium reached a peak of 10.7 mgm. per 100 cc. Consequently, on October 8th, 10th and 12th Parathormone was omitted, while on the intervening days, October 9th and 11th, only 12.5 units were given. The blood serum calcium began to drop immediately, and on October 12th reached 7.6 mgm. per 100 cc.

TABLE I

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925					
9.28	12.5 u	Lact. 1.0	8.1	None	Symptoms of Tetany.
29	25 u (12.5x2)	None	7.6	"	Comfortable
30	37.5 u (12.5x3)	"	7.2	"	Comfortable.
10.1	37.5 u	"	8.4	"	35 cc. Serosanguinous fluid removed from wound.
2	37.5 u	"	8.4	"	Comfortable.
3	25 u (12.5x2)	"	8.7	"	Comfortable.
4	25 u	"	"	"	Comfortable.
5	12.5 u	"	9.7	"	Patient ambulatory.
6	None	"	9.3	"	Basal Metabolism 13.8% plus.
7	12.5 u	"	8.2	"	Comfortable.
8	None	"	10.7	"	38 cc. Serosanguinous fluid removed from wound.
9	12.5 u	"	9.1	"	Comfortable.
10	None	"	"	"	Comfortable.
11	12.5 u	"	"	"	Queer sensations in body muscles.
12	None	"	7.6	"	Comfortable.
13	25 u	"	7.4	"	Occasional pain in legs and arms.
14	20 u	"	"	"	Occasional pain in legs and arms.
15	10 u	"	"	"	Comfortable.
16	25 u (12.5x2)	"	8.1	"	Comfortable.
17	25 u	"	"	"	Headache.
18	25 u	"	"	"	Comfortable.
19	50 u (25x2)	"	8.2	"	Comfortable.
20	None	"	10.5	"	Comfortable.
21	"	"	11.9	"	Comfortable.
22	"	"	"	"	Comfortable.
23	"	Lact. 3.0	8.4	"	Comfortable.
24	"	" 3.0	"	"	Comfortable.
25	"	" 3.0	"	"	Pain in right arm.
26	"	" 8.0	7.2	"	Pains in both arms—very hungry.
27	"	" 12.0	"	"	Comfortable.
28	10 u	" 12.0	"	"	Slight pain in right arm.
29	10 u	" 5.0	8.4	"	Comfortable.
30	None	" 5.0	"	"	Discharged from hospital.
31	10 u	" 5.0	"	"	
11/1	None	" 5.0	"	"	
2	10 u	" 5.0	"	"	
3	None	" 5.0	"	"	
4	10 u	" 5.0	8.8	"	
5	None	" 5.0	"	"	
6	10 u	" 5.0	8.8	"	
7	None	" 5.0	"	"	
8	10 u	" 5.0	"	"	
9	10 u	" 5.0	"	"	
10	10 u	" 5.0	"	"	
11	10 u	" 5.0	"	"	
12	10 u	" 5.0	"	"	
13	10 u	" 5.0	8.7	"	
					OPD Note: Quite comfortable since discharge.

## CHAPTER II. (October 12th to November 4th, 1925.)

During this succeeding period of three and a half weeks (see Chart No. 2), the following interesting events occurred: The blood serum calcium having reached the low level of 7.4 mgm. per 100 cc. on October 13th, daily Parathormone injections were resumed, varying from 10 to 50 units daily, most of the doses being 25 units per day. The last injection of this series was given on October 19th and consisted of 50 units. On this day the blood serum calcium was found to be 8.2 mgm. per 100 cc. Again, fearing a cumulative action of the Parathormone which might send the blood calcium to a dangerously high level, further injections were temporarily discontinued. That this decision was a wise one is borne out by the fact that the preceding seven days' injections, totaling 180 units, resulted in an elevation of the blood serum calcium to 10.5 mgm. on October 20th and 11.9 mgm. on October 21st (despite the fact that no Parathormone was

TABLE II  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925					
11/14	10 u	Lact. 5.0		None	
15	10 u	" 5.0		"	
16	10 u	" 5.0		"	
17	15 u	" 5.0		"	
18	10 u	" 5.0		"	
19	15 u	" 5.0	8.8	"	Having some cramps. Cold produces "accoucher" hand
20	15 u	" 5.0		"	
21	10 u	" 5.0		"	
22	10 u	" 5.0		"	
23	15 u	" 5.0		"	
24	15 u	" 5.0		"	
25	15 u	" 5.0		"	
26	15 u	" 5.0		"	
27	15 u	" 5.0	8.5	"	
28	15 u	" 5.0		"	
29	15 u	" 5.0		"	
30	15 u	" 5.0		"	
12/1	20 u	" 5.0		"	
2	15 u	" 5.0		"	
3	20 u	" 5.0	8.6	"	OPD Note: Occasional cramp Rt. foot
4	15 u	" 5.0		"	
5	20 u	" 5.0		"	
6	15 u	" 5.0		"	
7	20 u	" 5.0		"	
8	20 u	" 5.0		"	
9	20 u	" 5.0		"	
10	20 u	" 5.0		"	
11	20 u	" 5.0	7.8	"	OPD Note: Occasional minor cramps
12	20 u	" 5.0		"	
13	20 u	" 5.0		"	
14	20 u	" 5.0		"	
15	20 u	" 5.0		"	
16	20 u	" 5.0		"	
17	20 u	" 5.0		"	
18	20 u	Lact. 6.5	8.3	"	Trousseau xxx. Gained 23 pounds since 10-30-25.
19	20 u	" 6.5		"	
20	20 u	" 6.5		"	
21	20 u	" 6.5		"	
22	20 u	" 6.5		"	
23	20 u	" 6.5		"	
24	20 u	" 6.5		"	
25	20 u	" 6.5		"	
26	20 u	" 6.5		"	
27	20 u	" 6.5		"	
28	20 u	" 6.5		"	

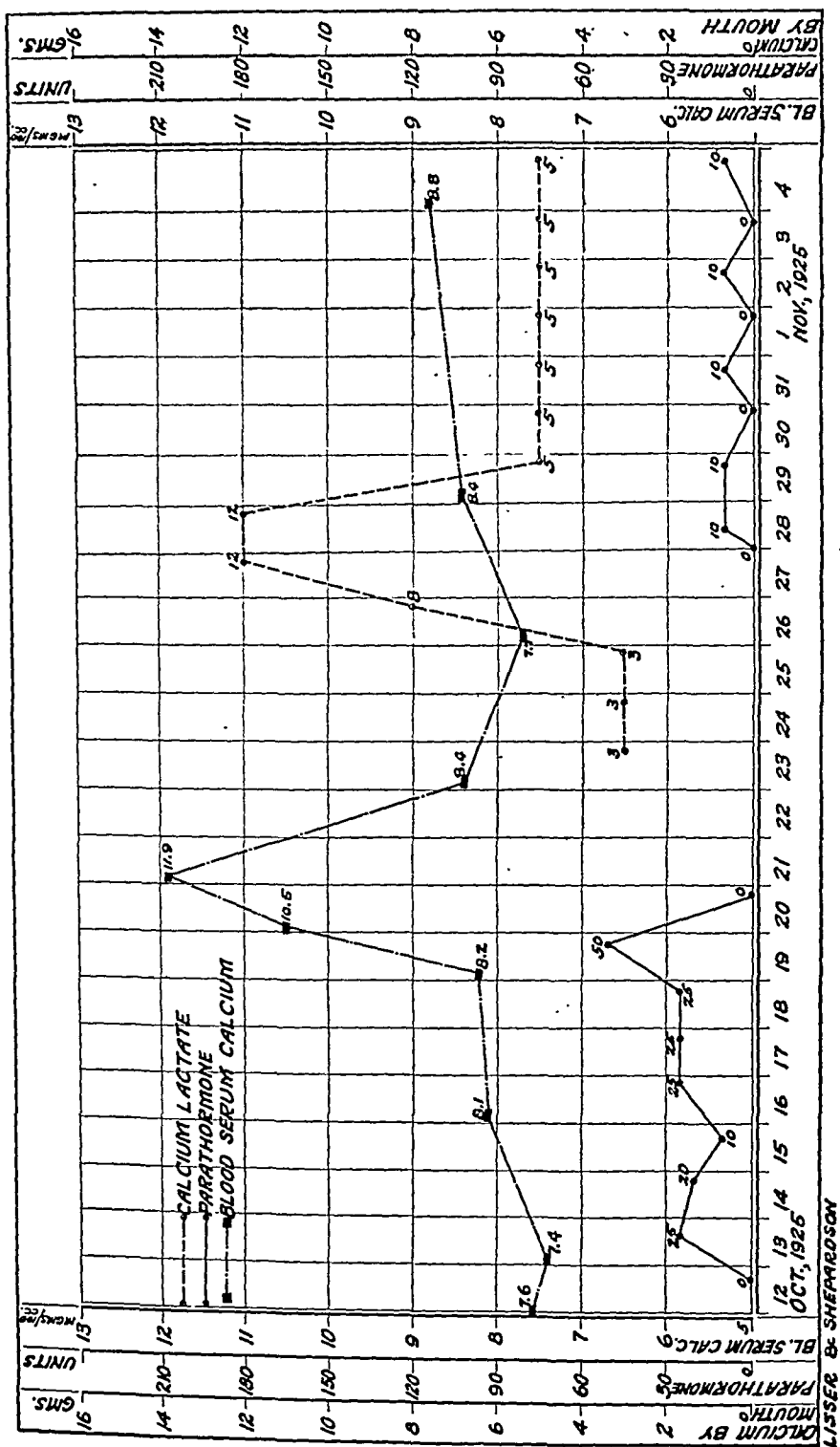


CHART 2

LISSER & SHEPARDSON

administered on either October 20th or 21st). However, this high level was not long maintained; by October 23rd it had dropped to 8.4 mgm. per 100 cc. It was then thought advisable to observe the effect of calcium lactate alone (given orally). Three grams were administered on October 23rd and also on the 24th and 25th. Apparently this was without effect on the blood serum calcium, for on the morning of the 26th it had dropped still further to 7.2 mgm. per 100 cc. On October 26th the calcium lactate was increased to 8 grams, and on October 27th she received 12 grams. However, the following day her fasting blood serum calcium was only 8.4 mgm. per 100 cc.

It became evident that it would probably be impossible to force the blood serum calcium to normal by means of oral administration of calcium lactate alone, and in view of the fact that the patient was again having symptoms, such as cramps in her feet and arms, together with some paraesthesiae, the calcium lactate was, on October 29th, reduced to 5 grams daily, and 10 units of parathyroid extract was given every other day.

The patient was discharged from the hospital on October 30th, having been carefully instructed in the hypodermic administration of parathyroid extract, of which she was to give herself 10 units every other day. In addition, she was to continue taking calcium lactate by mouth, 5 grams daily in divided doses. Under this regime her blood serum calcium reached 8.8 mgm. per 100 cc. on November 4th.

### CHAPTER III. (*November 5th, 1925, to January 17th, 1926.*)

This period of two and a half months may be likened to a plateau stage. She was at home reporting every week or two to the Ductless Gland Clinic of the Out-Patient Department. If this chapter were charted graphically, it would present a very monotonous picture, and is therefore better studied in the appended tables. For about half of this period the patient took 5 grams daily of calcium lactate orally, and during the latter half 6.5 grams daily. It was soon found that Parathormone had to be administered every day. At first 10 units sufficed, but this soon had to be increased to 15 units, then to 20 units, and finally to 30 units per day. Even with this increased dosage the blood serum calcium was never above 8.8 mgm. per 100 cc., and at one time dropped as low as 7.8 mgm. per 100 cc. Aside from some minor cramps in her hands and feet, the patient was quite comfortable for two and a half months; that is, until January 17th.

It is already apparent, from the foregoing, that the patient's tolerance for the hormone had gradually increased. It will be recalled that at the outset of her illness less than 30 units per day, over a period of one week, was sufficient to raise the blood serum calcium to 11.9 mgm. per 100 cc. This is in striking contrast to the slightly subnormal level of 8 to 9 mgm. per 100 cc. maintained by daily doses of 20 to 30 units over a period of two and a half months (not to mention the additional factor of 5 to 6.5 grams of calcium lactate per day).

## CHAPTER IV. (January 17th to February 10th, 1926.)

On January 16th the patient reported to the Clinic; she was decidedly weak, although able to get about. She suffered from transitory paresthesias and a very definite cramping of the thumbs. It was thought advisable to have her under closer scrutiny, and she was therefore again placed in hospital on January 18th. Blood serum calcium on the following morning was 8.2 mgm. per 100 cc. Inasmuch as the patient was restless and complained of smothering sensations, the Parathormone dosage was increased, in the hope of elevating the blood serum calcium, but despite 40 units daily

TABLE III  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1925 12/29	20 u	Lact. 6.5		None	
30	20 u	" 6.5		"	
31	30 u	" 6.5		"	
1926 1/1	20 u	" 6.5		"	Felt dizzy—sick—cough—mild bronchitis.
2	30 u	" 6.5		"	
3	20 u	" 6.5		"	
4	30 u	" 6.5		"	
5	20 u	" 6.5	8.1	"	OPD Note: Eye muscles feel stiff Trousseau x.
6	30 u	" 6.5		"	
7	20 u	" 6.5		"	
8	30 u	" 6.5		"	
9	20 u	" 6.5		"	
10	30 u	" 6.5		"	
11	20 u	" 6.5		"	
12	30 u	" 6.5		"	
13	30 u	" 6.5		"	
14	30 u	" 6.5		"	
15	20 u	" 6.5		"	B.M.R. 8.1% plus.
16	30 u	" 6.5		"	OPD Note: Gained 33 pounds since 10-15-25.
17	20 u	" 6.5		"	Occasional parasthesias and cramp of thumb.
18	30 u	" 6.5		"	Re-entered hospital—weak but am- bulatory.
19	40 u (20x2)	" 6.5	8.2	"	Restless—smothering feeling.
20	40 u (20x2)	" 1.5		"	
21	40 u (20x2)	" 2.5		"	
22	50 u (20x30)	" 3.0	7.3	"	Pains in arms.
23	100 u (50x2)	" 3.0		"	Restless—silly—some dizziness—in- somnia.
24	100 u (50x2)	" 3.0		"	Convulsion — twitching — labored breathing.
25	100 u (30,40,30)	" 3.0	7.7	"	Pains in shoulders and arms. Weight 103.6 kgm.
26	100 u (30,40,30)	" 3.0		"	Twitching of muscles—left shoulder.
27	100 u (30,40,30)	" 3.0		"	Same.
28	None	" 2.0	7.7	"	Same.
29	"	Brom. 3.0		"	Comfortable.
30	"	" 4.0		"	Comfortable.
31	"	" 6.0		"	Comfortable. Weight 100.1 kgm.
2/1	"	" 6.0	9.2	"	Comfortable.
2	"	" 6.0		"	Comfortable.
3	"	" 4.0		"	Ate very little.
4	"	" 4.0		"	Comfortable.
5	"	" 4.0	7.9	"	Comfortable.
6	"	" 6.0		"	Comfortable.
7	"	" 6.0		"	Comfortable. Weight 98.3 kgm.
8	"	" 6.0		"	Ate very little.
9	"	None	8.5	"	Headache—sodium Br. 8.0.
10	"	"		"	Sodium Br. 8%. Ate little.
11	75 u	Brom. 2.0		"	Fever Began. See Fig. IV. Unco- operative.
12	200 u (100x2)	" 3.0	6.7	"	Ate little—skin tender.
13	100 u	" 6.0		"	Muscle spasm—slight chill.

for the next three days the calcium content of the blood serum dropped to 7.3 mgm. per 100 cc. on the morning of January 22nd.

Clinically she appeared worse, and complained of pains in her arms; she was restless, unable to sleep, rather silly in her actions, twitched, and appeared to be on the verge of outspoken tetany. We thereupon, with some trepidation, embarked on more radical Parathormone dosage and injected 500 units in the next five days, an amount we would not have dared to give earlier (see Chart No. 3). We were surprised and disappointed to find that this enormous dosage was without immediate effect as far as her blood serum calcium was concerned, although it resulted in decided clinical improvement.

On January 28th (following five daily doses of 100 units of Parathormone) the blood serum calcium was only 7.7 mgm. per 100 cc. Fearing that the patient had acquired a sort of "fastness" to Parathormone, we discontinued it temporarily and resorted to calcium bromide orally. The latter was started on January 29th in doses of 4 to 6 grams daily. On February 1st the serum calcium reached 9.2 mgm. per 100 cc. In all likelihood this was the delayed cumulative effect of the huge doses of Parathormone administered the latter part of January. This assumption was borne out by the prompt drop in calcium to 7.9 mgm. per 100 cc. on February 5th and 8.5 mgm. per 100 cc. on February 9th. We concluded that the calcium bromide was having little if any influence on the blood calcium level. However, during the period of calcium bromide therapy (January 29th to February 8th, when no Parathormone was administered), the patient was relatively comfortable. It occurred to us that this might be due to the bromide rather than the calcium element. In order to test this, calcium was omitted and 8 grams of sodium bromide were given on February 9th and again on February 10th. This strategy was promptly abandoned, however, with the appearance of fever on February 11th. Here-with begins a new episode; to be described in the succeeding chapter.

#### CHAPTER V. (*February 11th to February 23rd, 1926.*)

In view of what follows, it is important to reiterate that no Parthormone had been administered from January 28th to February 10th, inclusive. On February 11th a febrile period began which lasted from three to four weeks, the maximum temperature never exceeding 38.6° centigrade (see Charts 4 and 5). Not knowing what complications might be developing, and fearing that the fever might have an unfavorable effect on the calcium metabolism, Parathormone injections were immediately resumed on February 11th. On this day 75 units was given. On the following morning, February 12th, the blood serum calcium had dropped to the critical level of 6.7 mgm. per 100 cc. Having in mind the increased tolerance which our patient had acquired for Collip's parathyroid extract, we dared not trifle with ordinary doses, and therefore administered 200 units



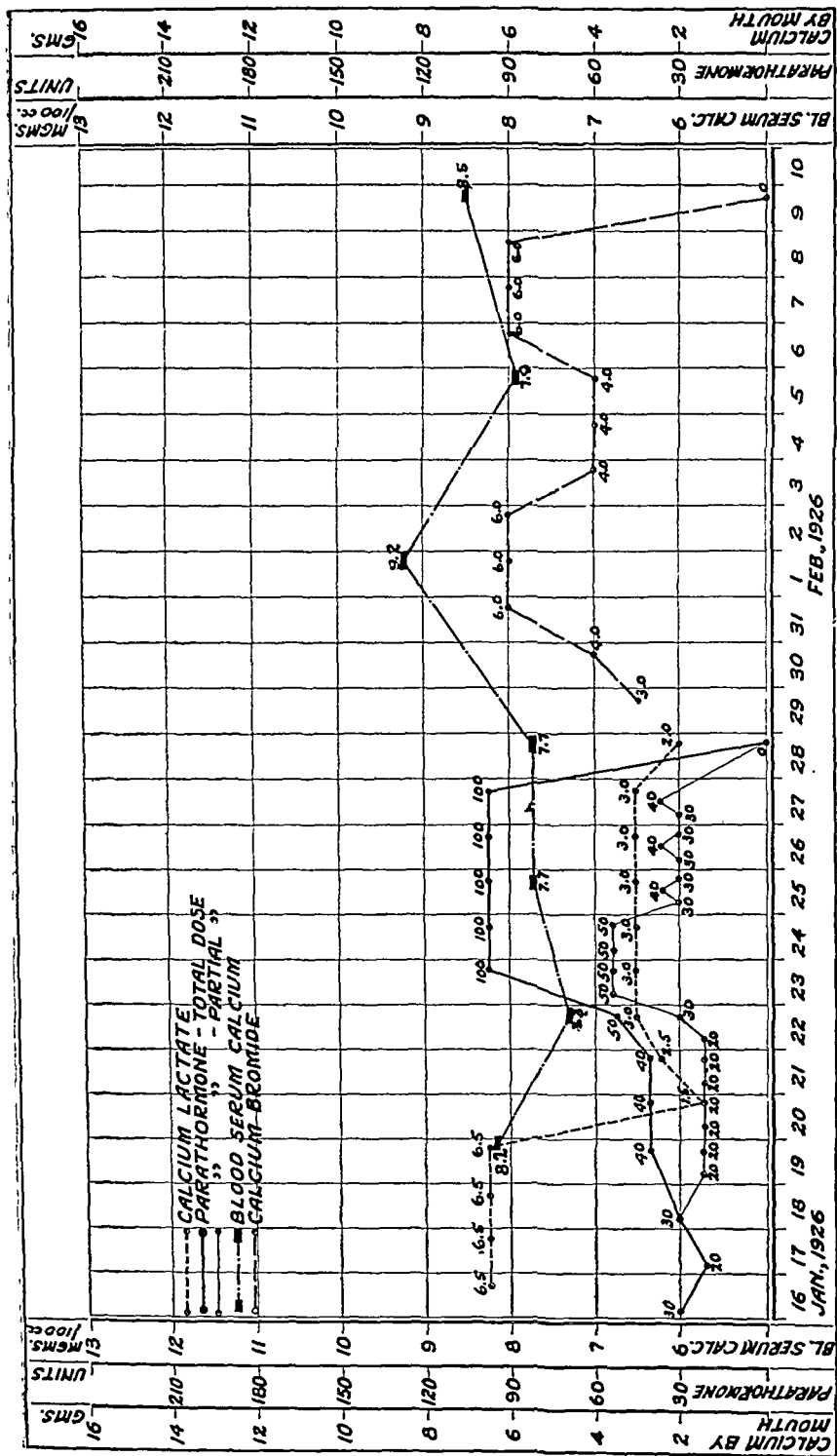


CHART 3

LISSER & SHEPARDSON

within the next 24 hours (see Chart 4). One hundred units was given on February 13th and again on February 14th and 15th. On February 16th 200 units was injected, making a total of 775 units within six days. On the morning of February 17th, blood serum calcium was found to be 8.8 mgm. per 100 cc. Two hundred units more of Parathormone was given on February 17th and again on February 18th. We were disappointed to find that on the morning of the 19th the blood serum calcium had dropped to 7.7 mgm. per 100 cc. Two hundred units more was given on February 19th and 100 units on February 20th, 21st and 22nd. By the morning of

TABLE IV  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1928 2/11	100 u (20x5)	None		None	Trembling of body—having headaches daily.
15	100 u (20x5)	"		"	Fairly comfortable.
16	200 u (50x1)	"		"	Some nausea. Weight 95.8 kgm.
17	200 u (50x1)	"	8.8	"	Fairly comfortable.
18	200 u (50x1)	"		"	Pain in legs, back, arms, very irritable.
19	200 u (50x1)	"	7.7	"	Fairly comfortable.
20	100 u (25x1)	Brom. 4.0		"	Fairly comfortable.
21	100 u (25x1)	" 4.0		"	Twitching—headache—nausea. Wt. 94.7 kgm.
22	100 u (25x1)	" 4.0		"	Trembling—twitching of body and extremities.
23	100 u (25x1)	" 4.0	8.1	"	Headache—restless—chills—thirsty.
24	100 u (25x1)	" 6.0		"	Restless—vomited—alternately hot and cold.
25	100 u (25x1)	" 6.0		"	Vomited
26	100 u (25x1)	" 6.0	8.6	"	Crying and moaning loudly in night.
27	100 u (25x1)	" 6.0		"	Very irritable—almost irrational—vomited.
28	100 u (25x1)	" 6.0		"	Has been taking only liquids for several days.
3/1	100 u (25x1)	" 6.0		"	Irritable—very noisy.
2	100 u (25x1)	" 6.0		"	Quiet—apparently comfortable.
3	100 u (25x1)	" 6.0	10.4	"	Some solid food.
4	100 u (25x1)	Lact. 4.0		.13	Ate well—irritable—unmanageable.
5	100 u (25x1)	" 6.0		.13	Uncontrollable—unmanageable—severe pain.
6	75 u (25x3)	" 6.0	11.9	.13	Restrained—nauseated.
7	75 u (25x3)	" 6.0		1.3	Quiet.
8	75 u (25x3)	" 6.0		1.3	Restless.
9	50 u (25x2)	" 6.0	12.6	1.3	Fairly comfortable.
10	50 u (25x2)	" 6.0		.13	Vomited—moaning and crying.
11	50 u (25x2)	" 6.0		.13	Moaning.
12	50 u (25x2)	" 6.0		1.3	Headache—otherwise comfortable.
13	50 u (25x2)	" 6.0	10.8	.13	Fairly comfortable.
14	50 u (25x2)	" 6.0		.13	Restless—severe headache.
15	50 u (25x2)	" 6.0		.13	Fairly comfortable
16	50 u (25x2)	" 6.0	12.0	.13	Moaning—irrational in evening.
17	50 u (25x2)	" 6.0		.13	Restless—ate well.
18	50 u (25x2)	" 6.0		.13	Restless.
19	50 u (25x2)	" 6.0		.13	Pain and restlessness—headache.
20	50 u (25x2)	" 6.0		.13	Restless.
21	50 u (25x2)	" 6.0	12.2	.13	Fairly comfortable. Weight 91.3 kgm.
22	50 u (25x2)	" 6.0		.13	Fairly comfortable.
23	50 u (25x2)	" 6.0		.13	Noisy—restless.
24	50 u (25x2)	" 6.0		.13	Pain in back of neck.
25	50 u (25x2)	" 6.0		.13	Comfortable.
26	50 u (25x2)	" 6.0		.13	Some dyspnea.
27	50 u (25x2)	" 6.0		.13	Feeling well—ambulatory.
28	50 u (25x2)	" 6.0		.13	Comfortable.
29	50 u (25x2)	" 6.0	11.6	.13	Some pain in legs.
30	50 u (25x2)	" 6.0		.13	Some dyspnea and palpitation.
31	50 u (25x2)	" 6.0		.13	Comfortable.
4/1	50 u (25x2)	" 6.0		.13	Headache.
2	50 u (25x2)	" 6.0		.13	Comfortable.
3	50 u (25x2)	" 6.0		.13	Comfortable. Weight 89.4 kgm.

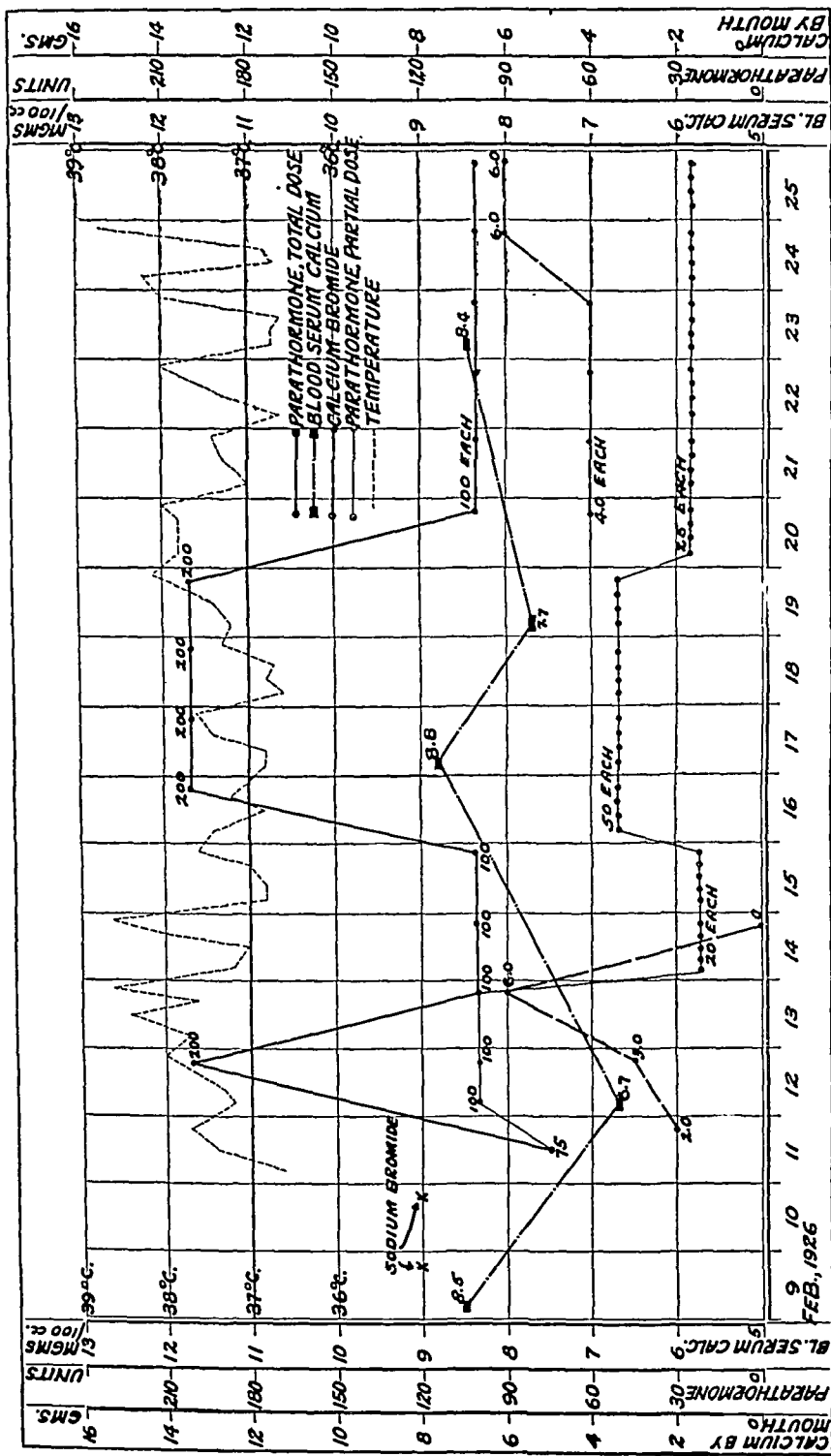


CHART 4

LISSER & SHEPARDSON

February 23rd the blood serum calcium had increased slightly to 8.4 mgm. per 100 cc.

In summarizing this chapter of twelve days intensive parathyroid therapy, one salient fact looms forth, namely, that 1675 units of Parathormone, an extraordinary amount, had little effect on the blood serum calcium. At the time we were inclined to attribute this to a remarkable increase of tolerance for this preparation. We knew it could not be due to a poor batch of the product, since all of it had been carefully standardized before delivery to us. Subsequent events disclosed that our assumption of increased tolerance was only partly responsible for the weak effect on the blood serum calcium. This will become apparent as the story progresses.

#### CHAPTER VI. (*February 23rd to March 16th, 1926.*)

It will be recalled that at the close of the preceding chapter the blood serum calcium level was 8.4 mgm. per 100 cc., and that the patient was receiving 100 units of Parathormone daily (hypodermically) and four grams of calcium bromide orally. A daily dose of 100 units of Parathormone intramuscularly and six grams of calcium bromide orally were continued from February 23rd to March 3rd. By this date the blood serum calcium had finally risen to the normal level of 10.4 mgm. per 100 cc. Calcium lactate was substituted for calcium bromide and 100 units of Parathormone was given on March 3rd, 4th and 5th. The following morning, March 6th, the serum calcium had reached 11.9 mgm. per 100 cc. Wishing to avoid a further rise to possibly dangerous heights, the Parathormone dosage was reduced to 75 units per day; three days later the blood serum calcium reached 12.6 mgm. per 100 cc.; whereupon the parathyroid extract was reduced still further to 50 units per day.

It was probably the subsidence and final disappearance of the fever which enabled us to maintain the blood serum calcium at a satisfactory level on the much smaller dose of 50 units of Parathormone per day. An additional therapeutic factor was introduced about this time, namely, 2 grains daily of dessicated thyroid substance. We were actuated to this procedure by the suspicion that some of the patient's symptoms might be due to a possible hypothyroidism which was masked by the parathyroid deficiency and not demonstrable by basal metabolic rate determinations. It is quite possible that the thyroid extract had a favorable effect of its own on the blood serum calcium and thus permitted smaller doses of Parathormone. We did not introduce it with this objective in mind, but the report of Aub and co-workers (23) confirms the impression we received at that time. In two cases of parathyroid tetany, Aub encountered a similar experience, and he concluded that in tetany due to low blood calcium, thyroid extract raises the blood calcium level as well as increases the calcium excretion. He gave it as his opinion that thyroid substance constitutes a therapeutic adjunct in this disease. However this may be, the combined use of 50 units

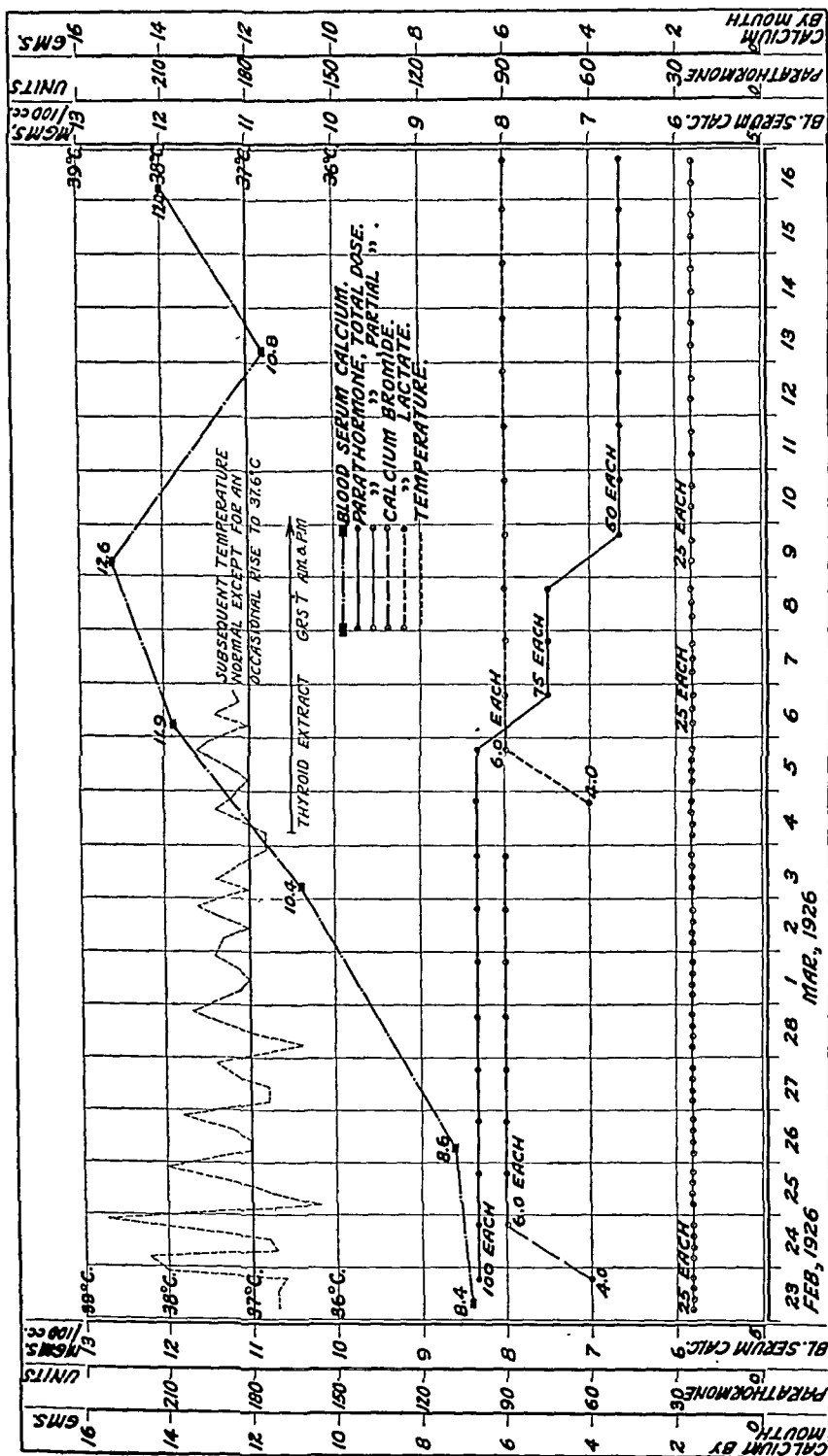


CHART 5

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of Parathormone, 6 grams of calcium lactate, and 2 grains of desiccated thyroid extract per day, resulted in a blood serum calcium level of 10.8 mgm. per 100 cc. on March 13th and 12 mgm. per 100 cc. on March 16th (see Chart 5).

During the five weeks embraced in Chapters 5 and 6 and graphically portrayed in Charts 4 and 5, little occurred in the patient's clinical status to warrant comment. She was irritable at times, and even irrational and unmanageable; restraint had to be resorted to. Whether this mental excitability was due to the fever or to tetany is difficult to state. Her behavior often suggested hysteria, or possibly a toxic psychosis. The cause of the fever was never explained.

TABLE V  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
1/1	50 u (25x2)	Lact. 6.0	10.8	.13	Some restlessness—headache.
5	50 u (25x2)	" 6.0		.13	Comfortable—ate well.
6	50 u (25x2)	" 6.0		.13	Comfortable.
7	50 u (25x2)	" 6.0		.13	Slight nausea.
8	50 u (25x2)	" 6.0		.13	Comfortable—wept in sleep
9	50 u (25x2)	" 6.0		.13	Comfortable.
10	50 u (25x2)	" 6.0		.13	Comfortable.
11	50 u (25x2)	" 6.0		.13	Screaming with pain in muscles— hysterical.
12	50 u (25x2)	" 6.0		.13	Still has pain in shoulder.
13	50 u (25x2)	" 6.0		.13	Pain all over body.
14	50 u (25x2)	" 6.0	10.1	.13	Comfortable.
15	50 u (25x2)	" 6.0		.13	Comfortable.
16	50 u (25x2)	" 6.0		.13	Pain in body.
17	50 u (25x2)	" 6.0		.13	Stupid—drowsy. Not eating well.
18	50 u (25x2)	" 6.0		.13	Comfortable. Weight 90.6 kgm.
19	50 u (25x2)	" 6.0		.13	Comfortable.
20	50 u (25x2)	" 6.0		.13	Comfortable.
21	50 u (25x2)	" 6.0		.13	Contracture left hand—opisthotic— cyanotic—hysteria.
22	50 u (25x2)	" 6.0		.13	Restless—see text.
23	50 u (25x2)	" 6.0		.13	Pains all over body. Hysterical.
24	50 u (25x2)	" 6.0	8.8	.13	Fairly comfortable. Weight 91.8 kgm.
25	50 u (25x2)	" 6.0		.13	Noisy in sleep.
26	50 u (25x2)	" 6.0		.13	Fairly comfortable—some generalized pain.
27	50 u (25x2)	" 6.0		.13	Nervous—excited—attack of body rigidity.
28	50 u (25x2)	" 6.0		.13	Some pain in shoulder.
29	50 u (25x2)	" 6.0		.13	Comfortable.
30	50 u (25x2)	" 6.0		.13	Attack of hysteria. See text.
5/1	75 u (25x3)	" 6.0		.13	Comfortable. Weight 91.9 kgm
2	75 u (25x3)	" 6.0		.13	Severe muscular pains.
3	75 u (25x3)	" 6.0		.13	Comfortable.
4	75 u (25x3)	" 6.0		.13	Comfortable. Not eating well.
5	75 u (25x3)	" 6.0		.13	Comfortable. Not eating well.
6	75 u (25x3)	" 6.0		.13	Attack of hysteria and pain.
7	75 u (25x3)	" 6.0		.13	Comfortable.
8	75 u (25x3)	" 6.0		.13	Comfortable. Weight 92.7 kgm.
9	75 u (25x3)	" 6.0	9.3	.13	Parathyroid Implantation.
10	75 u (25x3)	" 6.0		.13	Parathyroid Implantation.
11	75 u (25x3)	" 6.0		.13	Fairly comfortable.
12	75 u (25x3)	" 6.0		.13	Pain in abdominal muscles.
13	75 u (25x3)	" 6.0		.13	Fairly comfortable.
14	75 u (25x3)	" 6.0		.13	Fairly comfortable.
15	75 u (25x3)	" 6.0		.13	Fairly comfortable.
16	75 u (25x3)	" 6.0		.13	Fairly comfortable.
17	75 u (25x3)	" 6.0		.13	Fairly comfortable.
18	50 u (25x2)	" 6.0	11.6	.13	Fairly comfortable.
19	50 u (25x2)	" 6.0		.13	Fairly comfortable.
20	50 u (25x2)	" 6.0		.13	Fairly comfortable.
21	50 u (25x2)	" 6.0		.13	Fairly comfortable.

## CHAPTER VII. (March 16th to September 12th, 1926.)

This lengthy period of six months is condensed into one chapter of our narrative, because it again, like Chapter III, resembled a plateau stage, without extraordinary occurrences. For the first two and half months the patient remained in hospital and was for the most part fairly comfortable, except for occasional outbreaks of an hysterical nature. We could not believe that her emotional excitability was a manifestation of tetany, since her blood serum calcium throughout this time remained fairly high, ranging from 12.2 mgm. per 100 cc. on March 22nd to 8.8 mgm. per 100 cc. on May 3rd, most of the other determinations being above 10 mgm. per 100 cc. (which is average normal).

Realizing that the characteristic effect of Parathormone consists in mobilizing calcium, and fearing that its continuous administration over a

TABLE VI  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
5/21	50 u (25x2)	Lact. 6.0	9.2	.13	Fairly comfortable.
22	50 u (25x2)	" 6.0		.13	Fairly comfortable.
23	50 u (25x2)	" 6.0		.13	Fairly comfortable. Weight 91.9 kgm.
24	50 u (25x2)	" 6.0		.13	Some hysteria—slightly irrational.
25	50 u (25x2)	" 6.0		.13	Comfortable.
26	50 u (25x2)	" 6.0		.13	Some hysterical crying.
27	50 u (25x2)	" 6.0		.13	Comfortable.
28	50 u (25x2)	" 6.0		.13	Some nervousness toward evening
29	75 u (25x3)	" 6.0		.13	Comfortable.
30	75 u (25x3)	" 6.0		.13	Comfortable. Weight 93.7 kgm.
31	75 u (25x3)	" 6.0		.13	Comfortable.
6/1	75 u (25x3)	" 6.0	9.2	.13	Comfortable.
2	75 u (25x3)	" 6.0		.13	Discharged from hospital.
3	75 u (25x3)	" 6.0		.13	
4	75 u (25x3)	" 6.0		.13	
5	75 u (25x3)	" 6.0		.13	
6	75 u (25x3)	" 6.0		.13	
7	75 u (25x3)	" 6.0		.13	
8	75 u (25x3)	" 6.0		.13	
9	75 u (25x3)	" 6.0		.13	
10	75 u (25x3)	" 6.0		.13	OPD Note: Feeling fairly well.
11	75 u (25x3)	" 6.0	8.1	.13	
12	75 u (25x3)	" 6.0		.13	
13	75 u (25x3)	" 6.0		.13	
14	75 u (25x3)	" 6.0		.13	
15	75 u (25x3)	" 6.0		.13	
16	75 u (25x3)	" 6.0		.13	
17	75 u (25x3)	" 6.0		.13	
18	75 u (25x3)	" 6.0		.13	OPD Note: Has been comfortable.
19	75 u (25x3)	" 6.0		.13	
20	75 u (25x3)	" 6.0		.13	
21	75 u (25x3)	" 6.0	8.1	.13	
22	75 u (25x3)	" 6.0		.13	
23	75 u (25x3)	" 6.0		.13	
24	75 u (25x3)	" 6.0		.13	
25	75 u (25x3)	" 6.0		.13	
26	75 u (25x3)	" 6.0		.13	Notices teeth getting softer.
27	75 u (25x3)	" 6.0		.13	
28	75 u (25x3)	" 6.0		.13	
29	75 u (25x3)	" 6.0		.13	
30	75 u (25x3)	" 6.0		.13	
7/1	75 u (25x3)	" 6.0		.13	
2	75 u (25x3)	" 6.0		.13	
3	75 u (25x3)	" 6.0		.13	
4	75 u (25x3)	" 6.0		.13	
5	75 u (25x3)	" 6.0		.13	
6	75 u (25x3)	" 6.0		.13	

period of six months might be depriving the bones of their normal calcium content, x-ray studies of the pelvis and femur were made. No rarification of the osseous structures was revealed. These roentgenograms were taken in April, 1926. In this connection it may be mentioned, however, that two months later the patient volunteered the information that her teeth were getting softer.

Seven months had transpired since the onset of her illness, during which time it was necessary continuously to administer increasingly larger doses of Parathormone. There was no end in sight. A recent report (24) of a successful transplantation of a human parathyroid in a case of chronic tetany had come to our attention. Accordingly it was thought advisable to attempt parathyroid transplantation in the hope of achieving a successful graft and thus obviate the necessity for further injections of Parathor-

TABLE VII  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm / Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926					
7/7	75 u (25x3)	Lact. 6.0		.13	
8	75 u (25x3)	" 6.0		.13	
9	75 u (25x3)	" 8.0		.13	Chvostek xx. Cramps of eye muscles
10	75 u (25x3)	" 8.0		.13	
11	75 u (25x3)	" 8.0		.13	
12	75 u (25x3)	" 8.0		.13	
13	75 u (25x3)	" 8.0		.13	
14	75 u (25x3)	" 8.0		.13	
15	75 u (25x3)	" 8.0		.13	
16	75 u (25x3)	" 8.0		.19	OPD Note: Better since increasing calcium.
17	75 u (25x3)	" 8.0		.19	
18	75 u (25x3)	" 8.0		.19	
19	75 u (25x3)	" 8.0		.19	
20	75 u (25x3)	" 8.0		.19	
21	75 u (25x3)	" 8.0		.19	
22	75 u (25x3)	" 8.0		.19	
23	75 u (25x3)	" 8.0		.19	OPD Note: Feels and looks fine
24	75 u (25x3)	" 8.0		.19	
25	75 u (25x3)	" 8.0		.19	
26	75 u (25x3)	" 8.0		.19	
27	75 u (25x3)	" 8.0		.19	
28	75 u (25x3)	" 8.0		.19	
29	75 u (25x3)	" 8.0		.19	
30	75 u (25x3)	" 8.0		.19	
31	75 u (25x3)	" 8.0		.19	
8/1	75 u (25x3)	" 8.0		.19	
2	75 u (25x3)	" 8.0		.19	
3	75 u (25x3)	" 8.0		.19	
4	75 u (25x3)	" 8.0		.19	
5	75 u (25x3)	" 8.0		.19	
6	75 u (25x3)	" 8.0		.19	
7	75 u (25x3)	" 8.0		.19	
8	75 u (25x3)	" 8.0		.19	
9	75 u (25x3)	" 8.0		.19	
10	75 u (25x3)	" 8.0		.19	
11	75 u (25x3)	" 8.0		.19	
12	75 u (25x3)	" 8.0		.19	
13	75 u (25x3)	" 8.0	6.8	.19	OPD Note: Attacks of weakness—ap- prehension. Entered hospital with tetanic attack Semistuporous. Discharged from hospital.
14	100 u (25x4)	" 8.0		.19	
15	100 u (25x4)	" 8.0		.19	
16	100 u (25x4)	" 8.0		.19	
17	100 u (25x4)	" 8.0		.19	
18	100 u (25x4)	" 8.0		.19	
19	100 u (25x4)	" 8.0		.19	
20	100 u (25x4)	" 8.0		.19	OPD Note: Feels calm



none. Aside from its scientific interest, there was another motive which prompted us to this action, namely, a desire to reduce what might in another patient become a heavy financial burden.\* If one studies the appended table, it will be noticed that the blood serum calcium had gradually fallen from 12.2 mgm. per 100 cc. on March 22nd to 8.8 mgm. per 100 cc. on May 3rd. The daily therapy during this time had been the same throughout, except for an increase to 75 units of Parathormone per day two days prior to the relatively low serum calcium level of 8.8 mgm. per 100 cc. (May 3rd).

This increased dosage was decided upon because of one severe and two mild convulsive attacks, characterized by marked painful carpopedal spasms in which both arms and hands were twisted around to the middle of the

TABLE VIII  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926 8/21	100 u (25x4)	Lact. 8.0		.19	
22	100 u (25x4)	" 8.0		.19	
23	100 u (25x4)	" 8.0		.19	
24	100 u (25x4)	" 8.0		.19	
25	100 u (25x4)	" 8.0		.19	
26	100 u (25x4)	" 8.0		.19	
27	100 u (25x4)	" 8.0	7.2	.19	Chvostek x.
28	100 u (25x4)	" 8.0		.19	
29	100 u (25x4)	" 8.0		.19	
30	100 u (25x4)	" 8.0		.19	
31	100 u (25x4)	" 8.0		.19	
9/1	100 u (25x4)	" 8.0		.19	
2	100 u (25x4)	" 8.0		.19	
3	120 u (30x4)	" 8.0		.19	Chvostek xxx.
4	120 u (30x4)	" 8.0		.19	
5	120 u (30x4)	" 8.0		.19	
6	120 u (30x4)	" 8.0		.19	
7	120 u (30x4)	" 8.0		.19	
8	120 u (30x4)	" 8.0		.19	
9	120 u (30x4)	" 8.0		.19	
10	120 u (30x4)	" 8.0		.19	
11	120 u (30x4)	" 8.0		.19	
12	120 u (30x4)	" 8.0		.19	Entered hospital 9 P. M.
13	50 u (25x2)	" 3.0		.19	Comfortable.
14	100 u (25x4)	" 3.0		.19	Comfortable.
15	75 u (25x3)	" 3.0		.19	Convulsion—See text.
16	105 u (40x2.25)	" 3.0	6.6	.19	Dizzy.
17	160 u (40x4)	" 3.0		.19	Comfortable.
18	160 u (40x4)	" 4.0		.19	Pain in side—convulsions—See text.
19	160 u (40x4)	" 4.0		.19	Comfortable
20	160 u (40x4)	" 4.0	6.5	"	High fever—See Fig. VI—convulsions
21	160 u (40x4)	" 4.0		"	Vomiting after each meal.
22	160 u (40x4)	" 4.0		"	Vomiting.
23	160 u (40x4)	" 4.0	6.9	"	Nervous—restless.
24	160 u (40x4)	" 4.0		"	Fair day.
25	160 u (40x4)	" 3.0		"	Fair day.
26	160 u (40x4)	" 4.0		"	Restless—eyes feel queer.
27	160 u (40x4)	" 4.0		"	Fair day—occasionally has diplopia.
28	160 u (40x4)	" 3.0		"	Fair day.
29	160 u (40x4)	" 3.0	6.5	"	Fair day.
30	160 u (40x4)	" 4.0		"	Convulsion—See text. Bld. Cult. Neg.
10/1	160 u (40x4)	" 3.0		"	Fair day.
2	80 u (40x2)	" 4.0		"	Pain—numbness of hands—convulsions.
3	25 u	" 4.0		"	2.5 cc. 10% Ca Cl <sub>2</sub> intravenous—two convulsion.
4	160 u (40x4)	" 4.0		"	Abscess on thigh drained yesterday.
5	160 u (40x4)	" 1.0		"	Comfortable.
6	160 u (40x4)	" 4.0		"	Screaming.
					Several convulsions.

\*We were indebted to Dr. Wm. J. Kerr, Professor of Medicine, for a research grant which permitted the free use of a hospital bed together with an ample supply of Parathormone.

back, while the lower extremities were rigidly extended, with toes spread apart. These cramps seemed to be very painful. The peculiar attitude of the arms and hands was the opposite of the characteristic contractions of tetany. We suspected that they might be hysterical.

On May 10th, a parathyroid gland was quickly transferred from a patient undergoing thyroidectomy to the ventral abdominal muscles of our patient. The following morning the blood serum calcium was found to be 9.3 mgm. per 100 cc. This slight rise is better attributed to the recently increased Parathormone dosage (from 50 to 75 units per day) than to the transplanted gland. Another human parathyroid gland was grafted into the body wall on May 11th. On May 17th, six days later, the blood serum calcium had reached 11.6 mgm. per 100 cc. It is possible, though merely a speculation, that this rise of over 2 mgm. per 100 cc. was due to the parathyroid transplants. However this may be, the rise was a transitory one, for the blood serum calcium fell to the former level of 9.2 mgm. per 100 cc. five days later. It is equally possible that the parathyroid transplants had no influence on either the rise or subsequent fall, since it will be noted in the appended tables that the 75 units of Parathormone per day had been reduced to 50 units daily immediately after the blood serum calcium reached 11.6 mgm. per 100 cc.

The patient was discharged from the hospital on June 2nd and was followed in the Ductless Gland Clinic of the Out-Patient Department for the succeeding three and a half months. During this time it was necessary to increase the Parathormone to 75 units per day, and during the last month of this period to 100 units, and finally to 120 units per day. The dose of calcium lactate was also increased from 6 grams to 8 grams per day, and the dessicated thyroid from 2 grains to 3 grains per day. Despite this increased dosage of all three therapeutic constituents, the blood serum calcium steadily diminished from 11.6 mgm. per 100 cc. on May 17th to 8.1 mgm. per 100 cc. on June 25th, and still further to 6.8 mgm. per 100 cc. on August 13th. It was at this time that the daily Parathormone injections were increased from 75 units to 100 units. This was necessitated not only by the low calcium level, but also by an outspoken attack of tetany, in which the patient was semistuporous and which necessitated three days' hospitalization. During the succeeding month 100 units, and finally 120

TABLE IX  
A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S  
PARATHYROID EXTRACT

Date	Parathormone	Calcium Gm./Day	Blood Serum Calcium Mgm./100 cc.	Thyroid Substance	Clinical Status
1926 10/7	160 u (40x4)	Lact. 3 0		None	Convulsion.
8	160 u (40x4)	" 3 0		"	Irrational—several convulsions.
9	160 u (40x4)	" 3 0		"	In coma part of evening.
10	160 u (40x4)	" 3 0		"	In coma all night.
11	None	None		"	Died 12:10 P. M.

units of Parathormone per day was barely sufficient to keep the patient in reasonable comfort. She seemed to be constantly on the brink of tetany. It was, therefore, decided on September 12th to hospitalize her again, for what proved to be the last time.

### CHAPTER VIII. (*September 12th to October 11th, 1926.*)

Three days after entering the hospital the patient developed the first of several epileptiform attacks. They were not Jacksonian in type and certainly not tetanic.

Redlich (25) collected 72 cases in which epilepsy occurred with tetany, 21 being associated with tetania parathyreopriva following strumectomy (as in our case). In this latter group he believed the tetany etiologically responsible for the epilepsy.

Blood serum calcium had reached the critical level of 6.6 mgm. per 100 cc.; consequently Parathormone dosage was again increased, to 160 units per day. This amount was administered daily thereafter for the following 25 days, with the exception of 80 units on October 2nd and 25 units on October 3rd. This dosage was without effect on the blood serum calcium, which remained between 6.5 and 6.9 mgm. per 100 cc.

This inefficacy was in all probability largely due to the occurrence of another febrile episode, for on September 20th the patient's temperature rose rather abruptly to 40° C. The temperature curve can be followed on Chart 6. White blood count on September 20th was 13,350, with 90 per cent polymorphonuclears; 14,900 on September 21st, with 92 per cent polymorphonuclears; and a terminal rise to 34,450, with 90 per cent polymorphonuclears on the day of her death, October 11th. Blood culture on September 30th proved to be negative. On October 4th an abscess in the anterior aspect of the left thigh was incised and 30 cc. of pus withdrawn, culture of which proved to be staphylococcus aureus. This abscess apparently resulted from a self-administered dose of Parathormone given sometime before entering the hospital. Physical examination findings throughout this period were normal, except for this abscess. The patient very likely died of staphylococcus sepsis.

#### AUTOPSY REPORT\*

Complete autopsy was performed, including examination of the bone marrow and examination of the brain and spinal cord. Only positive findings will be mentioned here.

*Heart:* Weighed 420 grams; coronary arteries were prominent but not tortuous or thickened. The heart was extremely soft, as were all the tissues of the body. There was some slight atheroma about the aortic valves and the coronary orifices, otherwise the ascending aorta was elastic and smooth.

Microscopically, the epicardium was normal. The fasciculi of muscle were moderately uniformly separated but no fibrosis was present. The separation appeared due to a moderate diffuse edema.

\*The autopsy was performed by Dr. Leonard Buck and microscopic examinations by Dr. G. Y. Rusk, Professor of Pathology. The writers are indebted to them for the report, excerpts of which are given verbatim.

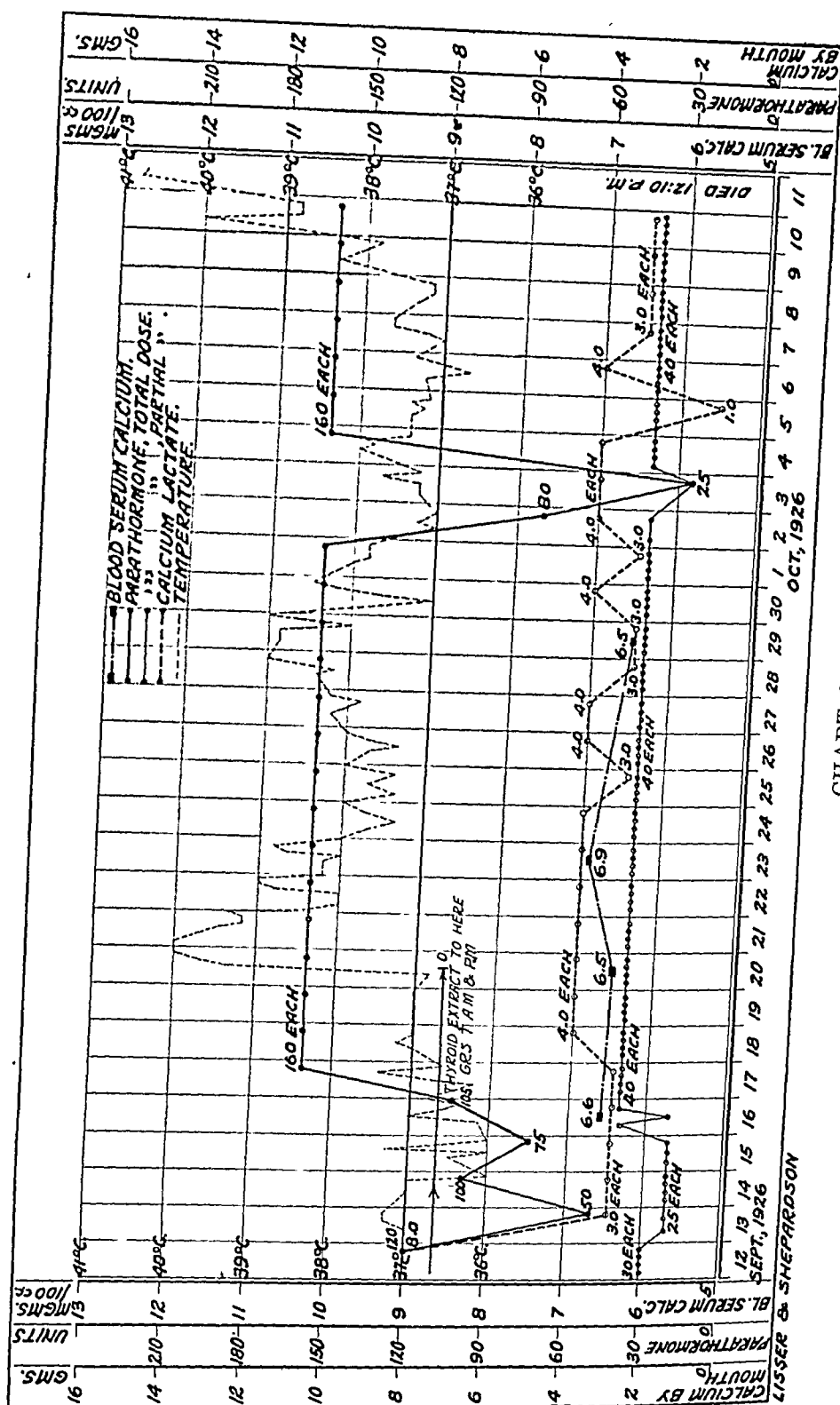


CHART 6

The gross and microscopical examination of the *lungs* showed a marked edema combined with a moderate diffuse dilatation of the capillaries. In no place was any evidence of inflammatory reaction seen.

The *liver* weighed 1900 grams and was smooth and pinkish-brown. Microscopically, the portal spaces occasionally contained a few lymphocytes. The liver cells showed a finely reticulated cytoplasm. The cells tended to be larger than normal and generally appeared separated and bulbous. This process was seen in cloudy swelling. The sinusoids showed a slight dilatation, otherwise were normal.

The *gall bladder* contained about 30 cc. of light brown bile and 17 pyramidal-shaped gall stones, together weighing 50 grams.

The *spleen* was large, weighing 500 grams. It was 15 cm. in length, 12 cm. in width and 5 cm. in height. Microscopically, the Malpighian bodies varied in size from normal to small. The lymphocytes appeared normal. The arterioles associated with the Malpighian bodies showed hyalin change. The sinusoids in some areas appeared dilated. The pulp elements showed moderate diffuse atrophy with fine diffuse fibrosis.

The *kidneys* were approximately the same size and shape and weighed 440 grams. Microscopically, the capsule appeared normal. The epithelium of the convoluted tubules showed foci of necrosis, also in places the epithelium was eosinophilic where the nuclei were still preserved. Casts occurred in some of the tubules. The interstitial tissue appeared edematous and rarely there was a slight focal increase of interstitial fibrous tissue. Here a few lymphocytes were present.

The gross and microscopic appearance of the *gastro-intestinal tract* was normal, except for some black superficial pigment found in the lower part of the peritoneum, dotted behind the appendix and in the pelvis.

*Bone marrow*: Microscopically, showed diffuse cellular hyperplasia affecting both the myelocytic elements and the red cells. There were a relatively fairly large number of bone marrow multinucleated cells.

*Lymph nodes*: Microscopically, sections from various lymph nodes from the abdominal cavity showed general edema. The lymph nodules were indistinct and there was rather marked endothelial hyperplasia.

*Brain*: The convolutional markings were normal. The leptomeninges and Pacchionian bodies were normal. The basal vessels showed a few very small plaques of atherosclerosis. The covering of the brain was normal. There was a small amount of dark material on the roof of the 4th ventricle. The vessels in the region of the right dentate nucleus were congested with blood. On section of the right cerebral hemisphere there was seen a necrotic-like area in the anterior part of the lenticular nucleus extending throughout its posterior 2/3. The structure in this region was mush-like in consistency. No hemorrhagic staining was seen and it probably was an artifact from poor fixation. There was no reaction about this softening.

#### THE DUCTLESS GLANDS

The trachea, larynx, and tongue with their surrounding tissue were removed and on section several nodules approximately 1 cm. in diameter were found on the left side of the trachea, which on cut section appeared to be thyroadenoma.

*Thyroid*: Showed considerable variation in the size of the alveoli. The colloid was unusually abundant. The cells of the thyroid appeared slightly reduced in size. The nuclei stained deeply and the cytoplasm was scanty. Intersecting the glandular elements there were bands of connective tissue. In association with these especially there were small alveoli with little or no evidence of hyperplastic alteration. Areas of diffuse hyalin degeneration occurred; also areas showing the remnants of old interstitial hemorrhage with phagocytic cells bearing pigment. There was a striking lack of the lymphocytic infiltration which accompanies hyperplastic goiters.

Two sections of the abdominal wall were removed under the scars originating from the implantations of *parathyroid* into the recti muscles. Grossly, nothing was seen, except scar tissue and no evidence of parathyroid structure was found microscopically. Careful search failed to reveal parathyroid tissue anywhere in the body.

*Thymus*: It was an enlarged two-lobed thymus covering the upper part of the pericardium, 1 cm. thick, about 10 cm. wide and 8 cm. long. Microscopically the thymus showed small groups of lymphocytes, appearing rather diffuse as if lying in an edematous background. In these lymphocytic areas there was an additional Hassel corpuscle which appeared quite hyalinized.

*Hypophysis:* Appeared of normal size. The sinusoides appeared irregularly congested. The glandular portion showed (hematoxylin and eosin stain) the general architecture of the gland to be normal. A very few of the alveoli contained cells which were rather small with scanty cytoplasm. In general the cells were of normal size with neutrophilic cytoplasm, intermingled with which, here and there, were cells, slightly larger in size, showing eosinophilic cytoplasm. Other alveoli were lined entirely with eosinophilic type but the predominating alveolus was lined with the neutrophilic type. There appeared to be a normal proportion between these two types of cells. The pars intermedia showed alveoli lined by cells with smaller darker nuclei, cuboidal in shape, with indefinitely staining cytoplasm. Small accumulations of colloidal material occurred in some of these gland spaces. The amount of pars intermedia appeared normal and no alteration was seen in the structure. The pars nervosa appeared quite normal.

*Pineal:* Was found to be a smooth, irregular granular-like body 5x3 mm.

*Adrenals:* The cortex appeared normal. In the center of the gland there was an excessive number of chromatic cells, staining orange color in hematoxylin and eosin. There was also present in the cortex, several more or less circumscribed masses of cortical cells showing marked vacuolation of the cytoplasm due to accumulations of lipoidal material.

*Pancreas:* Was grossly and microscopically normal.

*Uterus:* The endometrium showed edema in the more superficial portions. The glands appeared moderately reduced in number. The myometrium was normal.

*Ovaries:* Showed no noteworthy change.

The Pathologist was impressed by two significant points: First, the complete absence of parathyroid tissue; and, second, by the evidence of intense sepsis. The autopsy was essentially negative in all other respects.

#### SUMMARY AND COMMENTS

A case of tetania parathyreopriva has been described, in which three parathyroid glands were accidentally removed in the course of strumectomy. Under energetic substitution therapy consisting of increasingly large doses of Parathormone, aided by calcium and thyroid substance orally, this patient was kept alive for one year. Death was probably due to staphylococcus sepsis. Complete autopsy was performed. Careful search failed to reveal any parathyroid tissue.

We were therefore dealing with complete absence of a ductless gland over a period of one year. Inasmuch as neither the clinical course nor the subsequent autopsy findings revealed any noteworthy secondary disturbance in any of the other ductless glands, it would seem reasonable to assume that the parathyroid glandules have very little relation to the other members of the hormonopoietic system. In this respect one is reminded of the disease diabetes mellitus, which, if it be due, as is generally supposed, to a deficiency of the internal secreting portion of the pancreas, is likewise unaccompanied by secondary alterations in the other ductless glands. This is in rather striking contrast to other outspoken uniglandular deficiencies (such as myxedema, eunuchism, and hypophyseal infantilism), or hyperfunctional endocrinopathies (such as exophthalmic goiter, acromegaly and the precocity syndromes due to tumors of the epiphysis cerebri, the adrenal cortex and the gonads), where several glands are eventually involved.

Probably the most significant feature of this year-long treatment with a standardized potent parathyroid extract was the increased tolerance or

immunity which the patient developed toward this product. It became more and more difficult to maintain the blood serum calcium at approximately a normal level, despite the administration of progressively larger doses of Parathormone. In fact, during the last month of the patient's illness 160 units per day failed to raise the serum calcium above 6.9 mgm. per 100 cc. Snell (10) in a recent personal communication mentions an experience in a case of tetania parathyreopriva similar to ours. Hunter (19) includes a personal communication from Aub to the same effect. It would seem that in severe protracted cases of parathyroid deficiency substitution therapy with Collip's hormone, even when combined with liberal doses of calcium, barely suffices to keep the patient alive.

Consequently, when the additional strain of a mild intercurrent infection, which under normal circumstances would be readily withstood, is added, the prognosis is extremely bad. One is at once reminded of the similar condition in diabetes mellitus in which the severity of that disease is markedly increased by mild infections, and just as insulin dosage must then be tremendously increased, so likewise under similar circumstances must Parathormone dosage be augmented. It is interesting, however, that no immunity follows long-continued insulin administration. The increased tolerance which we have stressed in the case of Parathormone may be due to its protein constituent. Possibly a further purification of the extract will eliminate this drawback.

#### CONCLUSIONS

1. Complete absence of the parathyroid glands for over a year failed to produce any clinical or autopsy evidence of secondary disturbance in the other ductless glands. In this respect, chronic tetania parathyreopriva resembles diabetes mellitus.

2. Although Collip's parathyroid hormone is a biologically standardized product which is promptly beneficial in acute parathyroid tetany, its effectiveness in chronic tetany, where daily injections are necessary for many months, is seriously impaired by an increasing immunity toward the product gradually acquired by the patient. This may be due to an increased tolerance for its protein content.

3. Intercurrent infections in chronic tetany demand augmented Parathormone dosage, just as they do increased insulin dosage when they complicate diabetes mellitus.

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# NOTE ON CALCIFICATION IN PITUITARY ADENOMAS

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The differential diagnosis of tumors in the pituitary region, whether they are primarily intrasellar or extrasellar, hinges largely upon the roentgenological features of the case; and the presence or absence of calcification in the lesion has an importance second only to that of the deformations of the pituitary fossa.

Since approximately three out of every four of the tumors that arise from rests of the craniopharyngeal duct show shadows of calcification, the presence of such shadows within or adjacent to the sella is strongly in favor of one of these lesions, particularly if the tumor syndrome has occurred in childhood. It is well known, however, that congenital tumors of this nature may remain latent until adult life or middle age at which time new growth of other sorts are more prevalent.

Particular difficulties of diagnosis arise when the chiasmal syndrome of optic atrophy with bitemporal field-defects indicating a local tumor is associated with a sella turcica that is neither enlarged nor deformed. The presence of calcification in the suprasellar tumors that evoke this now well recognized symptom complex whether in children or adults speaks particularly in favor of a craniopharyngeal duct tumor. One, nevertheless, may be misled by shadows of suprasellar calcification that are cast by a psammomatous meningioma, by an aneurysm, by a slowly growing glioma, or even by an adenoma.

Though demonstrable calcification in a pituitary adenoma is rare, it must be taken into consideration in the preoperative diagnosis of the tumors of this important neighborhood, whether they arise within and expand the sella or lie largely above it. It is the purpose of this report to briefly comment upon these cases.

In a review of the roentgenological reports of the 285 verified adenomas in Dr. Cushing's series, it was found that abnormal shadows had been described in some 50 or more instances most of them having unmistakably been cast by residual fragments of eroded clinoid processes or by hyperostoses of the pituitary floor. With the exclusion of all such cases, there remains a group of 19 cases in which the shadows within or just above the pituitary fossa seemed to imply actual calcium deposition within the body of the tumor itself. In this small group of cases there were no constant factors. They compressed seven chromophile adenomas and twelve of chromophobe or mixed types. Ten of the patients were males, nine were females, and the average age was thirty-seven. There was no possible correlation with the probable duration of growth nor with the microscopic

appearance of the lesion. The duration of clinical symptoms varied from one to twenty years.

The site of such calcification cannot be definitely known until suitable necropsies provide an opportunity for examination of the entire tumor specifically for calcification. There were no fatalities in this group of nineteen cases and the calcified area was in no instance identified at operation nor was calcification found on pathological examination of the tissue removed in any case. With but five exceptions the nineteen patients were all operated upon by the transphenoidal route which indicates that the sella was widely expanded and a preoperative diagnosis of adenoma had been made. Usually upon incising the tense dural capsule, soft adenomatous tissue extrudes itself and after a specimen has been taken for verification the larger and softer adenomas have been radically dealt with by suction. By this method of procedure the chances of securing for study the calcified portion of the tumor have been extremely small.

Occasionally in former years patients with an enlarged sella were operated upon by the transphenoidal route for a presumed adenoma and a craniopharyngeal pouch tumor was encountered. Probably all of these cases, in these days of more perfected roentgenography, would have shown calcification. Given a young adult, however, showing such calcification unassociated with enlargement of the sella, a diagnosis of craniopharyngeal pouch cyst is almost inevitable. Even when the sella is expanded one may easily be misled as is shown by the following two examples.

**CASE 1. SURG. NO. 18904. CHROMOPHOBE ADENOMA MISTAKEN FOR CRANIO-PHARYNGEAL POUCH CYST. TRANSFRONTAL OPERATION. MARKED IMPROVEMENT IN VISION.**

*Admission:* May 26, 1923. Edward D., a student, aged 18, referred by Dr. J. G. Janney of Dodge City, Kansas, with the complaints of headache and failing vision.

*Clinical History:* Three years before admission the patient began to suffer from generalized headache and bitemporal failure of vision. As headaches became more severe they caused vomiting and were sometimes followed by twenty to thirty hours of deep sleep. For a year and a half he has noticed an increasing thirst and a corresponding increase in urinary output. During the past year he has gained twenty-five pounds in weight and has noticed an undue fullness of the breasts and hips. For the past few months he has had great difficulty in concentration and it is almost impossible for him to keep up with his classes.

*Examination:* The patient is overnourished and looks about fourteen years of age. The contour of his body and limbs and the distribution of hair is distinctly feminine. The genitalia are normally developed. Of local pressure signs he shows a bilateral primary optic atrophy with bitemporal hemianopsia, V.O.S. 20/100, V.O.D. 20/50. The basal metabolic rate averaged minus eight. Fluid intake and output showed a daily average of 2600 cc. Roentgen-ray examination showed a slightly turriccephalic cranial vault. The sella turcica was large and somewhat irregular. There was a small area of calcification just above the pituitary fossa.

Considering the age of the patient and the presence of suprasellar calcification, a preoperative diagnosis of craniopharyngeal pouch cyst was made.

*Operation:* June 9, 1923. The region of the chiasm was exposed by a right transfrontal osteoplastic flap. When the frontal lobe was elevated and the chiasm brought into view, a soft reddish mass was seen projecting up between the optic nerves. After incision of the dural capsule, a large amount of adenomatous tissue was removed and the chiasm and optic nerves freed from pressure.

*Postoperative Course:* Recovery was uneventful and vision improved rapidly. At the time of discharge, three weeks later, his vision was O.S. 20/50, O.D. 20/20 with normal fields.

*Pathology:* Sections showed irregular masses of epithelial cells between blood-filled spaces. The epithelial cells were large, with granular cytoplasm and prominent nuclei. No mitotic figures were seen. The cytoplasm was vacuolated and showed no definite granules other than mitochondria. No calcification was seen in the section.

*Diagnosis:* Chromophobe adenoma.

CASE 2. SURG. NO. 33916. CHROMOPHOBE ADENOMA IN A YOUNG ADULT. MISTAKEN FOR CRANIOPHARYNGEAL POUCH CYST. TRANSFRONTAL OPERATION.

*Admission:* May 7, 1929. Edward S., a clerk, aged 26, referred by Dr. Frederick Verhoeff of Boston with the complaint of failing vision.

*Clinical History:* He had always enjoyed perfect health up until one year ago at which time vision began to fail chiefly in the right eye. He was fitted with glasses which served well for about six months. Two months ago in spite of a second change of glasses, he became almost blind in the right eye. There had been no headaches, or other neurological symptoms. He stated that he had always been a little fat and rather overdeveloped about the hips and breasts. Though twenty-six, he needs to shave only once a week. Manifestations of libido have always been very slight.

*Examination:* Inspection showed a short, somewhat adipose young man. His breasts and hips were rather full, skin smooth and delicate, hair of feminine distribution. All deep reflexes were symmetrically hyperactive. There was an inequality of pupils, the left being the larger. His basal metabolic rate averaged minus eighteen. The local pressure signs found were primary optic atrophy (vision O.D. 20/100, O.S. 20/30) with a temporal hemianopsia in the right eye. Roentgen-ray examination showed the pituitary fossa to be considerably enlarged and expanded. The floor of the sella was depressed and the posterior clinoids were completely eroded. Just medial to the left anterior clinoid was seen a dense curvilinear shadow with multiple fainter shadows posterior to this, strongly suggesting calcification in the wall of a cyst.

The diagnosis lay between a craniopharyngeal pouch cyst and a congenital aneurysm.

*Operation:* May 24, 1929. The chiasmal region was exposed by a right transfrontal osteoplastic flap. On elevating the frontal lobe, the right optic nerve was found frayed out over the bulging pituitary capsule. Upon incision of the dural capsule, soft adenoma began to protrude. The tumor for the most part lay under the right optic nerve pushing this far upward and outward. A sufficient amount of adenomatous tissue was removed by rongeurs and suction to permit collapse of the capsule. At no time was any evidence of calcification met with.

*Postoperative Course:* The patient made a rapid recovery and was discharged three weeks later. There was, however, no improvement in visual acuity or filling out of his field defect in the right eye, up to the date of discharge.

*Pathology:* Sections show a very cellular structure consisting of wide bands of closely packed small epithelial cells. There is very little suggestion of architecture and the tissue is quite vascular. The great majority of the cells are of the chromophobe type. Mitotic figures are occasionally found. No calcification was seen in the sections.

*Diagnosis:* Chromophobe adenoma.

#### COMMENT

In the first case, an incorrect diagnosis was inevitable. In the second case, though the patient was well below the average age for adenomas, this diagnosis should have been more seriously considered. The roentgenograms of the sella were fairly typical of adenoma in spite of the definite calcification within it.

## SUMMARY

Nineteen verified pituitary adenomas have shown shadows of calcification in the roentgenograms. Other cases showing abnormal shadows about the sella have been excluded.

A review of the roentgenograms of these nineteen cases makes it seem fairly certain that the calcification actually lay within the adenoma. All types of adenomas (chromophile, chromophobe and mixed types) were represented in the nineteen cases.

The calcified area was not identified at operation, nor has calcification been detected in a careful review of the bits of tissue that were sectioned. The opportunity of studying an entire gland specifically for calcification was not afforded in this group of cases.\*

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\*It is possible, of course, that an adenoma and a small hypophysial duct tumor may co-exist and the shadows be produced by calcification in the latter lesion. However, since this paper went to press, we have observed calcification in a chromophobe adenoma on microscopical examination of the fresh tissue.

Harvey Cushing

# A CASE OF HEBEPHRENIC DEMENTIA PRAECOX WITH MARKED IMPROVEMENT UNDER THYROID TREATMENT\*

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In a previous article (1), a summarizing report was made of a series of studies on endocrine factors in dementia praecox. Among 80 patients studied, 14 presented evidence of thyroid deficiency. Of these, nine were diagnosed as definitely and five as probably hypothyroid. Eleven were treated with thyroid substance. In six of the 11, the diagnosis was explicit, and in the other five the evidence of endocrine deficiency was convincing, but the differential findings in some respects were ambiguous. Of the six definitely hypothyroid patients all showed significant mental improvement; four of the five regarded as probably hypothyroid became better. The initial prognosis in each case was unfavorable. Spatial limitations precluded publication of the multitudinous observations involved in the study of each patient. The following case history is presented, therefore, both as an interesting example of striking improvement under medication and as exemplifying the methods used in the research.

The methods are largely those developed by Rowe and his collaborators at the Evans Memorial in Boston (2). In addition to securing as complete family and personal histories as possible and of making careful routine physical examinations, various metabolic studies are made on each patient.

A quantitative analysis of two twenty-four hour samples of urine is made for total solids, total nitrogen, urea nitrogen, uric acid nitrogen, ammonium nitrogen, creatinin nitrogen, and residual nitrogen. In actual practice, the total solids, total nitrogen, and residual nitrogen are the three data of most significance. The ammonium nitrogen gives an index of possible loss of urea through ammoniacal decomposition, and thus casts a light on the dependability of the reported residual nitrogen, which is a derived figure dependent largely for validity on an accurate determination of the urea. In dealing with psychotic patients, there is always an element of uncertainty as to whether an actual twenty-four hour sample is secured. Catheterization as a routine measure is inadvisable because of its unfavorable psychological effect. The creatinin value is therefore of particular

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\*The cost of this research was defrayed in part by the Memorial Foundation for Neuro-Endocrine Research of Boston.

importance is affording a rough indication of the success in obtaining a true representative specimen. We frequently find it necessary to discard analyses in which the creatinin values fall outside normal limits. The total solids give an indication of the general level of metabolism, and the total nitrogen, of protein metabolism.

Even in a partial twenty-four hour sample, some idea of the level of protein metabolism can be obtained by comparison of the relative proportions of total nitrogen and creatinin nitrogen. We routinely calculate a TN/CN ratio. In the normal subject, with average protein intake, this ratio is about 28. Marked lowering of the ratio is, of course, indicative of protein inanition.

In addition to quantitative analyses, qualitative tests are also made for albumen, reducing substances, and urobilinogen, and microscopic studies are made of the urinary detritus. These may give an indication of serious disturbances of carbohydrate metabolism, of liver dysfunction, and particularly of nephroses or pseudo-nephroses suggestive of thyroid or adrenal deficiency.

As Rowe has emphatically reiterated, this diagnostic system requires the interpretation of each datum in the light of the presence or absence of all factors that may influence it in a quantitative way. Accordingly, the phenolsulphonephthalein output is determined on each patient as an index of the condition of the kidneys, which is potentially able to cause marked displacement of the levels of the various nitrogenous bodies. In short, in the presence of nephritis, the interpretation of the urinary, as well as the blood, chemical findings is quite different than in a case without this complication. Parenthetically, the limitations of the 'phthalein test are recognized.

Basal metabolism is carefully determined in each case. As previously pointed out (3), no little patience is required at times to obtain reliable readings in the case of psychotic subjects. Indeed, occasionally an instance arises in which, for the time being, a satisfactory determination cannot be made. Usually, however, with a few rehearsals, even timorous or recalcitrant patients will relax sufficiently to permit a fairly accurate test. We have various checks on the actual validity of the tests. Ordinarily, with each successive rehearsal, the oxygen consumption is lowered until an approximately constant level is reached. This is likely to be at the true basal level. However, during the course of the determination, both the pulse rate and the respiration rate are determined at brief intervals. In a true basal state, these figures remain essentially constant throughout the test. Any irregularity, therefore, is interpreted as indicating upward displacement from the true basal level. Moreover, the ward attendants record the early morning pulse rates of each patient. A comparison of the ward pulse rate and that obtained during the basal metabolism test obviously indicates whether or not the patient is in a state of actual repose. It is by no means always true that apparently satisfactory relaxation

actually indicates a basal state. The application of these various checks frequently prevents our being led astray by reports from the basal metabolism laboratory. When the first tests are unsatisfactory, repetitions are requested until either convincing evidence of their true basality is secured or it becomes evident that it is not then possible to secure a representative test.

The blood pressure and rectal temperature are routinely determined at each basal metabolism test. The significance of these as criteria of basality would seem to be too obvious to require comment.

Incidentally, these criteria are worthy of widespread adoption. It is no secret that many diagnosticians habitually accept basal metabolic reports at their face value, irrespective of their actual validity. In practice, it is probably true that such reports are as frequently misleading as they are informative. No physician should accept a basal metabolism report that does not include data on both pulse and respiratory rates throughout the period of the tests. He can readily determine for himself the normal rates as well as the blood pressure of his individual patient at rest in familiar surroundings when in a state of genuine repose and use these as criteria. Any report that fails to show constancy of pulse and respiration rates, normal blood pressure and temperature and, especially, a true resting pulse rate, should be disregarded or discounted in accordance with the extent of the vitiating deviations.

The blood morphology is studied in each case. The three data of special endocrine significance are presence or absence and degree of secondary anemia, of lymphocytosis, and of eosinophilia. Secondary anemia is much more characteristic of thyroid than of pituitary deficiency, which conditions may present confusingly similar pictures. Lymphocytosis is likely to be found in any type of endocrinopathy. Eosinophilia points toward pituitary rather than thyroid deficiency.

A chemical analysis of the blood is made for non-protein, urea, uric acid, and creatinin nitrogen, as well as for sugar. Characteristically, the non-protein, as well as the urea nitrogen, is normal in pituitary and ovarian deficiency, but trends upward in thyroid and adrenal deficiency. Uric acid, on the other hand, is typically high in pituitary and adrenal deficiency, but is normal in thyroid and ovarian deficiency. The blood sugar trend is low in adrenal and thyroid deficiency, but normal in pituitary and ovarian deficiency. In our experience, the most useful single datum is high blood uric acid, as differentiating pituitary from thyroid deficiency.

Likewise, especially significant in this regard, is the galactose tolerance. Almost none of the data in Rowe's system are individually pathognomonic. A high galactose tolerance, however, accompanying other signs of glandular deficiency, practically always means pituitary involvement.

The weight, height, trunk length, and chest circumference are determined for each patient. The weight deviations and the sitting-height index

are, of course, well known "constitutional" indicators, and their interpretation needs no special comment in this connection. They have not proved to be of much value in our studies of psychotic patients.

The "lung volume" is determined by the well known spirometer method. A priori, this datum should be of little or no significance, at least in psychotic patients. The amount of air that one is willing to exhale into the instrument would seem to be too much a matter of whim. In actual practice, however, the datum is of considerable importance, especially as an index of thyroid involvement. Shallow respiration is, of course, a well known sign of thyroid disease. In significant degrees of thyroid deficiency, in which the oxygen consumption is materially lowered, the patient seems to establish such a deep seated habit of restricted respiration that his spirometer reading is characteristically affected. Whatever be the explanation, it is an empirical fact that "lung volumes" substantially below prediction are highly indicative of thyroid rather than of other glandular deficiencies. In our practice, the normal volume is calculated to both the Dryer and the West standards, and the average deviation is taken as representing the condition actually present.

Alveolar carbon dioxide is routinely determined for each patient, though we have not been able to convince ourselves as yet that it is a significant datum in psychotic subjects. It is probable that by the use of a method whereby true alveolar air is certainly secured, the determination would be of some significance. It is planned later to introduce such a method.

The foregoing comprise most of the data routinely assembled. The Evans Memorial group have found it expedient to utilize a considerable number of supplementary tests, as determined by special indications in each patient. For the most part, we have not found it practicable to employ such tests in our particular situation. The deterrent factors are partly lack of resources and partly inability to secure adequate cooperation from the patients. In case of the more trying procedure, too, the psychological reactions of the subjects often demand consideration. Schizophrenic patients are prone to delusional misinterpretations and may be made significantly worse by unpleasant and uncomprehended test procedures.

We do, however, systematically make x-ray studies of the sinuses, stomach, and chest, and repeated fluoroscopic examinations for the determination of ptosis or stasis in the colon, and, secondarily, of constipation. Our earlier experiences suggested that liver dysfunction might play a significant rôle in dementia praecox, and for several months we routinely determined the direct and indirect Van den Bergh reactions, the bromsulphalein excretion, and made Graham tests on each patient. The results of the studies (as yet unpublished), however, indicate that liver dysfunction, at least as indicated by these tests, is not an important consideration, and they are no longer included in our routine procedures.



Having assembled the various data, they are first evaluated as to validity. Any demonstrable non-endocrine cause of a given deviation is regarded as vitiating that particular test. For example, eosinophilia in a patient with intestinal parasites has no value as indicating pituitary deficiency. The next procedure is to determine cumulatively the significance of the total mass of evidence. The methods of differential interpretation have been recently set forth by Rowe (4), and need not be reiterated here.

#### CASE REPORT

The patient, D. S., No. 38,042, an unmarried Armenian factory hand of thirty-four, entered the hospital on January 31, 1928. No significant *family history* is available. The *personal history* is scanty, and was derived through an interpreter from an uncle, whose acquaintance with the patient is not intimate. He was born in Armenia and arrived in the United States about 1913. In 1916 he returned to Europe and was in the French Military Service two years, fighting against the Turks. He then returned to this country and obtained work in Buffalo, New York.

The first manifestations of mental trouble appeared some two years before his admission to the hospital. While working in a restaurant, he complained that voices from the dishes were making trouble for him. An Armenian friend then brought him to Worcester and left him with a cousin. He worked for a short time in a coffee room, then became moody and silent and gave up his position to live with his cousin. He slept badly and would occasionally jump out of bed to explore the room. At times he laughed in a silly manner. He began to eat very sparingly and, if allowed, would stand all day in a corner, staring into space. He then became mute, disoriented, and unable to recall past events. He walked into a lake and called for help. He was afraid of noises.

On admission, physical examination disclosed no significant abnormalities except slight exophthalmos and hyper-active knee jerks. He was polite but appeared to be depressed and abashed by his new surroundings. He was partially oriented for time and place, and stated that he was bothered by noises. On the wards, where he soon fell in with the routine, he spent much of his time standing in one place, staring into space. He often laughed in a peculiar, silly manner. He was fairly cooperative and approximately oriented, but appeared generally depressed and apathetic. He was apprehensive, seclusive, preoccupied, and answered questions in an incoherent and irrelevant manner. He showed no insight, and poor judgment. The staff *diagnosis* was "hebephrenic dementia praecox."

On April 3, 1928, the case was reviewed by Dr. L. B. Hill, who confirmed the diagnosis of hebephrenic dementia praecox and recorded a bad *prognosis*, believing that eventual deterioration would be the patient's lot.

On May 28, 1928, the patient was transferred to the research ward for special study.

A blood Wassermann reaction was negative, and physical examination failed to disclose any significant abnormalities.

From urinalysis the protein intake was found to be at a low maintenance level, the residual nitrogen low normal, the total solids low, and the TN/CN index, 23. The basal metabolism was 79 per cent.\* The blood pressure was 106-64; the pulse, 54; the rectal temperature, 97.2°; and the respiratory rate 16-18. Conformity with ward observations as well as consistency of pulse and respiratory rates during the test indicated the validity of the basal rate reported.

The blood was normal as regards formed elements except for well marked secondary anemia. The blood chemical findings were normal, as were the 'phthalin output and the galactose tolerance. The weight closely approximated the calculated normal, but the "vital capacity" was only 76 per cent of the predicted value. A *diagnosis* of thyroid deficiency was recorded.

The findings just discussed are fairly typical of thyroid deficiency. An ideal picture, however, would include increased residual urinary nitro-

\*We find it convenient to follow Langfeldt (5) in expressing basal metabolism in absolute percentage of normal, rather than in plus or minus deviations as is the common, awkward practice. Thus, "79%" is the equivalent of "-21%."

gen, and lymphocytosis, as well as slightly lower basal metabolic rate and "vital capacity." Many endocrinologists would expect, too, a certain degree of obesity, but our experience with psychotic patients indicates that in this group obesity is not common in either thyroid or pituitary deficiency. The normality of weight and the moderate depression of the basal rate and lung volume were interpreted as signifying a relatively mild degree of the thyroid deficiency.

On June 23, 1928, thyroid treatment was initiated at a level of 6 grains, Burroughs & Wellcome preparation, daily. Subsequent experience in numerous other cases indicates that this dosage was well below a significant level. The dosage was gradually increased until 18 grains daily was reached on October 7.

The first apparent effect was an increase in the psychotic manifestations, and the picture became increasingly that of catatonia rather than hebephrenia. In July, the patient became very stubborn and resistive, talking to himself, and being easily angered. This change can be interpreted as significantly favorable, indicating a renewal of acute concern with inner problems; rather than a passive acceptance of the situation, which is an ominous feature characteristic of hebephrenia. Throughout the summer the patient continued mostly mute, dull appearing, seclusive, and depressed, but amenable to directions and able to do simple work in the cafeteria, until September, when, for a period, he refused to work. Late in the fall he became slightly more approachable.

On October 20, the various routine tests were repeated. They showed slightly more satisfactory protein metabolism, complete correction of the secondary anemia, and the development of mild lymphocytosis, but the findings were otherwise very similar to those noted in June. The thyroid dosage was obviously inadequate.

The dosage was therefore gradually increased until December 14, when a level of 33 grains daily of Armour's preparation was reached.\* A repetition of the diagnostic studies showed very moderate improvement of protein metabolism and an increase of the basal metabolic rate to 87 per cent. The blood pressure and temperature were slightly improved to 114/58, and 98.2°, respectively, but the pulse remained essentially unchanged. Secondary anemia was again reported, but this finding is so anomalous, in the light of other experiences (6), as to cast doubt on the accuracy of the determination. The patient had gained slightly in weight, and the lung volume had slightly decreased, though not significantly. The findings otherwise were surprisingly similar to those of October 20.

In November, the first significant evidence of mental improvement begins to appear in the notes of the various observers.† He began to speak spontaneously, to be more sociable and less antagonistic and dejected.

The gradual increase in medication continued to January 26, 1929, when a level of 48 grains of Armour's preparation daily had been reached. The patient showed a surprising failure to react physically. His ward pulse and temperature charts showed no significant changes during this period, and the weight was precisely that of October 6. The obvious suspicion arose that the patient was eluding the vigilance of the ward personnel and not actually ingesting the thyroid that was put into his mouth. We were unable, however, to secure any evidence that such was the case. As a routine measure in all cases at first, and later when there is any doubt of cooperation, the medicaments are placed in the patient's mouth, and he is compelled to swallow several sips of water and then open the mouth for inspection. At this time, we were left with a feeling of uncertainty whether the patient actually had a very high tolerance for thyroid or the ability systematically to deceive an experienced nurse. We have had other experiences indicating that schizophrenic patients often do have a remarkably high tolerance for this substance.

On January 26, 1929, an observation period of one month, without medication, was instituted. This resulted in no detectable shift in the average ward pulse and temperature curves, but was followed by a prompt loss of weight of five pounds, which persisted unchanged throughout the month. Beginning on

\*We are indebted to Armour & Company for generous supplies of material.

†Although confirmed by the authors, the testimony upon which this report is based is that of independent observers—a psychiatrist, a psychologist, and a nurse.

February 25, thyroxin by vein, one injection weekly, of 10 mgm. was begun, and carried through with one omission to May 21. The patient promptly reacted by loss of weight, this gradually decreasing from 120 pounds at the beginning to 105 pounds at the end of the period. The pulse and temperature, however, as recorded on the wards, were not perceptibly influenced. As determined by laboratory tests, also, the pulse and temperature, as well as the blood pressure, remained unaffected. The basal metabolism, as shown by these separate tests, promptly came up to normal, where it remained throughout this period, except that on April 2, following an interval of two weeks without medication, it had dropped to 85 per cent. During this period, the patient became more depressed and suspicious, and for a short period had to be tube-fed, though at the end of the period he had again begun to improve somewhat, being more accessible and less depressed. He impressed the observers as having become physically weak, though he was distinctly improved in this respect at the end of the period. Whether the weakness was due to the thyroid or to some undetected condition was not ascertained.

On March 6 the case was reviewed by the Hospital Staff and all but one member judged it to be one of catatonic dementia praecox. One psychiatrist thought that the mood swings shown at this time were more indicative of manic depressive psychosis.

The transformation of a hebephrenic to a catatonic picture might well be interpreted as a favorable development, the latter condition in common experience being the more likely to improve. The fact that sufficient affect had been regained to lead a competent psychiatrist to a diagnosis of manic depressive insanity is, of course, likewise favorable.

On May 27, a series of psychometric tests was attempted. The patient appeared to be willing but unable to comprehend problems. He worked slowly, and without any plans. It took him a long time to answer all questions. He was taciturn and occasionally while working made incomprehensible noises. Under these circumstances, an accurate appraisal was impossible, but the results, as they stood, indicated intelligence of imbecile grade. The mental age by the Stanford-Binet tests was 5 1/12, and the I. Q., 36.

On May 26, the intravenous medication was discontinued, and the oral use of Squibb's thyroxin in dosage of 0.8 mgm., t. i. d., was begun.\* The reaction to change of medication was prompt. Within three days the patient was reported as eating better, and becoming more alert at his work. The psychologist reported on June 1: "His attitude has apparently changed; he now tries to listen when he is spoken to; tries to do his part of the work; has quite enlisted the sympathy of the attendant and nurse on the ward; apparently he is putting up a fight to come back." His improvement was rapid. On June 19 he attended a baseball game, where he was interested, laughed, and had a good time. He was personally neater and helpful on the ward to the limit of his ability. He became amenable to re-educational psychotherapy, though he failed to show any definite evidence of insight as to his psychosis. He smiled with seemingly normal affect, and announced his purpose to cooperate with the hospital authorities to get well.

The thyroxin treatment continued unchanged to September 14. During the summer he was in a condition of maintained improvement. He was able to make friends on the ward, though he remained shy of strangers. He occasionally showed a depressed expression, though he was usually complacent. He answered readily when questioned and showed normal animation in facial expression. He was well oriented, and no evidence of hallucinations or delusions could be elicited. He became keenly interested in getting out of the hospital and going to work.

On August 7-8, the psychometric tests were repeated. The patient now showed fair cooperation, but was handicapped by language difficulty. His I. Q. was estimated at 55, as compared with 36 in May.

On August 13, his protein metabolism was fairly satisfactory, the protein intake being 60-65 grams. The basal metabolic rate was recorded as 86 per cent, but the blood pressure, pulse, and temperature remained as low as at the beginning. There was still a slight secondary anemia, and the lung volume was 22 per cent below prediction. Blood chemistry, 'phthalein output, and galactose tolerance were normal, but he remained 10 per cent underweight. The findings

\*A trial lot of a preparation manufactured by a new method by E. R. Squibb & Sons was employed. We wish to record our appreciation of the cooperation of this firm in supplying the drug.

were interpreted as indicating still some degree of thyroid or other glandular deficiency.

On September 14, the thyroid dosage was increased by the addition of 2 grains of Armour's preparation t. i. d., but the patient was discharged on trial visit on September 23, and the results of the increase were not determined.

At the time of his discharge he was still showing some tendency at times to depression, but was otherwise free of gross psychotic manifestations. It was the opinion of the psychiatrist who last examined him that he was not entirely well.

In view of the failure to secure complete normalizing of metabolism and of the ignorance, low mentality, and relatively friendless position of the patient, it is not unlikely that he will suffer a relapse and return to the hospital for further treatment, though if proper medical supervision with continuation of thyroid medication can be secured, the outcome may be entirely satisfactory.

We are not disposed to attempt any appraisal of the general significance of this report. The final determination of the significance of endocrine factors in dementia praecox must be determined statistically and with a much larger mass of evidence than is now available. While the case reported is by no means unique in our experience, it is, after all, a single case, and examples of unexpected improvement in dementia praecox are by no means rare. The outcome, at any rate, is strikingly better than was to have been anticipated under ordinary hospital treatment.

#### SUMMARY

The case is reported of an Armenian factory hand of 34, who had been suffering for at least two years of hebephrenic dementia praecox. The onset had been insidious, and a prognosis of further deterioration had been confidently made. He showed no significant gross physical abnormalities, but his protein metabolism was unsatisfactory, his pulse, blood pressure, temperature, basal metabolic rate, erythrocyte count, and "vital capacity" were low. The blood chemistry, galactose tolerance, and weight were normal. His case was diagnosed as one of thyroid deficiency. Under thyroid medication, the psychotic picture became more nearly that of catatonia, then strikingly improved toward normality. Repeated metabolic studies showed that the glandular deficiency was only partially corrected, but the improvement reached a stage justifying discharge from the hospital on trial visit. The case is reported as exemplifying results secured in several other instances.

Our thanks for cooperation are due to numerous fellow workers in the hospital, but especially to Superintendent W. A. Bryan, Dr. M. Yorshis, Mr. A. P. Guiles, Dr. D. A. Shakow, and Miss Anna Walsh.

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# A STUDY OF BLOOD SUGAR CURVES BEFORE AND AFTER THYROIDECTOMY\*

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The purpose of this paper is to present some interesting blood sugar curves taken before and after thyroidectomy and to study the changes in metabolism incident to surgery, particularly in respect to their bearing on the etiology of diabetes. During the past six years it has been our privilege to study the glycosuria and hyperglycemia occurring in a large number of patients presenting themselves for treatment because of symptoms of hyperthyroidism. In addition we have studied a smaller number of patients who came to us because of symptoms of diabetes but who also presented evidence of hyperthyroidism. In the first group a diagnosis of diabetes was made in a few instances and it is chiefly with these that we are concerned in this paper.

Space will not permit a review of the voluminous literature relative to the combined problem of diabetes and hyperthyroidism. Furthermore, a very complete review was made by John (1) in 1927 and by Lahey and Joslin (2) in 1928. Two previous reviews, one by Fitz (3) in 1921, and later, one by Wilder (4) are also outstanding.

Considerable variance in opinion apparently exists as to what constitutes true diabetes in the presence of hyperthyroidism. Both Fitz and Wilder were extremely cautious not to include any cases in their series wherein there was any doubt as to the presence of diabetes. Joslin and Lahey discarded from their report eleven cases ordinarily classified as diabetes and omitted nine more which they classified as potential diabetes. Their basis for doing so they clearly state: "For the present, therefore, and to avoid premature diabetic cures, we have raised the standard for the diagnosis of diabetes in hyperthyroidism to a blood sugar of 150 mgm. fasting or 200 mgm. or more after meals in addition to glycosuria." They felt that Wilder and Fitz must have used the same diagnostic standards, although this the latter did not specifically state.

Joslin and Lahey consider that hyperthyroidism alone is the factor in disease of the thyroid which leads to glycosuria and is distinctly more important than the accompanying increased metabolism, whereas Wilder states his position as follows: "The phenomena exhibited by patients with true diabetes combined with states of hyperthyroidism or hypothyroidism appear to be related to the general metabolic rate and are therefore susceptible of explanation without recourse to speculation as to a specific

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\*Read at the Thirteenth Annual Meeting of the Association for the Study of Internal Secretions, Portland, Ore., July 9, 1929.

interdependence of the thyroid and pancreas." John, on the other hand, states that the hyperglycemia and glycosuria associated with hyperthyroidism must be regarded as a functional diabetes with a definite disturbance of the insulogenic apparatus and presents evidence from which he concludes that the degree of hyperglycemia bears no relation to the severity of the hyperthyroidism or to the height of the basal rate.

A fundamental piece of work by Sanger (5) in 1922, in which he studied the respiratory quotient in patients with hyperthyroidism and in controls, led him to conclude that the increase in the respiratory quotient after giving glucose proves that individuals with a thyrotoxicosis burn carbohydrates more readily than normal individuals and inasmuch as their blood sugars remain elevated they obviously cannot be storing it. Thyroid fed animals after a certain period of time have very little liver glycogen even though they are fed on high carbohydrate diets.

We have, therefore, in hyperthyroidism, a liver poor in glycogen because of the insistent calls of the muscles for more glycogen because of the increased metabolism. A similar condition exists in diabetes mellitus, a liver low in glycogen, but for another reason, insufficient insulin to enable the liver and muscles to store it. Macleod (6), commenting on the work of Porges and Salomon, in which they determined the respiratory quotient in dogs in which the pancreas had been removed two days previous to the tying of the vessels of the liver, and found quotients ranging from 0.859 to 1.19, remarks that the chief interest of these results is to show that similar changes in R. Q. occur in completely diabetic animals as in normal ones, and when the influence of the abdominal viscera is removed, thus indicating, contrary to the belief of many, that the muscles in diabetes have not lost their power to oxidize carbohydrate. Joslin (7) states that it is becoming more and more evident that it is not so much the lack of the diabetic to utilize carbohydrate as lack of carbohydrate to utilize.

Hyperglycemia is characteristic of diabetes, whereas by no means is it always present in states of hyperthyroidism, as many patients with severe forms of thyrotoxicosis and high metabolic rates exhibit normal blood sugar curves. In patients, therefore, with hyperthyroidism in which hyperglycemia is present, it must be assumed, in order to explain the anomaly, that some disturbance of the insulogenic apparatus must be taking place. Neither Wilder's explanation, that in hyperthyroidism insulin is more rapidly destroyed, nor Sanger's, that toxic changes in the liver cells prevent storage, is satisfactory, else the hyperglycemia would bear a quantitative relationship to the hyperthyroidism.

Let us now consider the opinions of various authorities concerning the diabetic Anlage according to Naunyn's conception. Joslin (1) raises the question as to whether true diabetes ever occurs in hyperthyroidism unless this factor is present and says that one can hardly fail to reach the conclusion that if the diabetic Anlage were present to only a slight degree in

a patient, hyperthyroidism would bring it to the fore. John (8) quotes Naunyn as follows: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria only when there exists a predisposition to diabetes." And Von Noorden: "Pure hyperthyroidism in the presence of a fully normal chromaffin system will seldom produce an alimentary and spontaneous transitory glycosuria." Wilder (4) expresses himself in this way: "Patients with no diabetes and consequently with large supplies of insulin, reveal no lack of tolerance for carbohydrates, even when their metabolism is stimulated by extreme grades of hyperthyroidism because their supply of insulin is more than adequate." From this statement it might be implied that an abnormal blood sugar curve in the presence of hyperthyroidism suggests a potential diabetes. According to Joslin's statistics, an hereditary history of diabetes can be obtained in only about 25 per cent of diabetic patients. In his cases of hyperthyroidism and diabetes it was 20 per cent. Statistics are always open to question, despite the care with which they are taken, and are notably unreliable. Moreover, as pointed out by Joslin, the diabetic age zone is around 50 years. It is certainly possible that many potential diabetics may well die of other causes before reaching this age, or, having attained this age, an exciting cause of sufficient force may never have presented itself.

The efficiency of a blood sugar curve as a means of detecting a very mild potential diabetes, it has seemed to us, is open to question from the following point of view. May it not be that a diabetic Anlage of such a mild form may be present as to evade detection by our ordinary methods and be brought out into the open only by the development of hyperthyroidism in the patient? The blood sugar curves of two patients with mild diabetes uncomplicated by hyperthyroidism lends support to this contention (Charts 8 and 9).

In our group of true diabetes and hyperthyroidism there are twenty-four patients who were operated upon. Ten of these were of the parenchymatous and fourteen the adenomatous hyperplastic type. There was one death. Following operation, increase in tolerance was rapid and in some cases, remarkable in degree. We have included two patients (Charts 1 and 2) in this group who possibly should be placed in the potential diabetic group. Their histories will be discussed later.

Blood sugar curves before and after operation were determined on a series of twenty selected patients who showed glycosuria in addition to hyperthyroidism. Sections of the thyroid showed eight with parenchymatous and nine with adenomatous hyperplasia, and three with cystic colloid goiters. The blood sugar curves of only five showed failure to go below 150 mgm. at the end of the second hour. There was apparently no relationship between the type of thyroid disturbance in the toxic goiters and the curve.

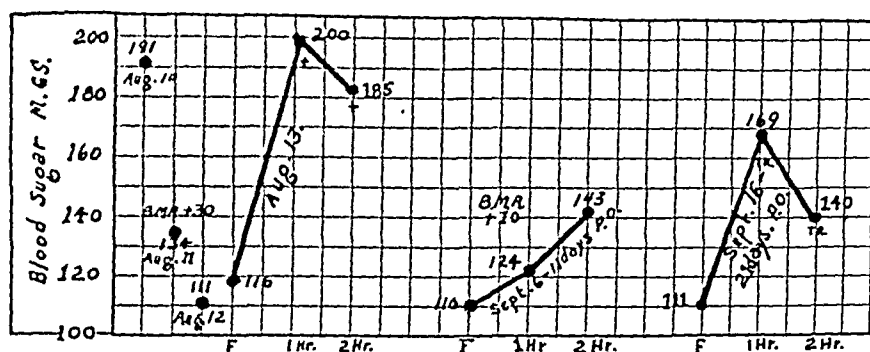
Using the diagnostic standards of Joslin and Lahey for the identification of diabetes associated with hyperthyroidism, we have included two

patients in our series of true diabetes, as stated above, who have shown, following thyroidectomy, return to approximately normal curves.

The first patient, case C. A. D. (Chart 1), age 56, housewife, came complaining of tachycardia, dyspnoea on exertion for two weeks, tremor of the hands for three months and weakness, sweating and loss of about ten pounds in a month. She stated that she had been eating considerable candy for three

CHART I

CASE—C. A. D. PATHOLOGICAL DIAGNOSIS—PARENCHYMATOUS AND ADENOMATOUS HYPERPLASIA

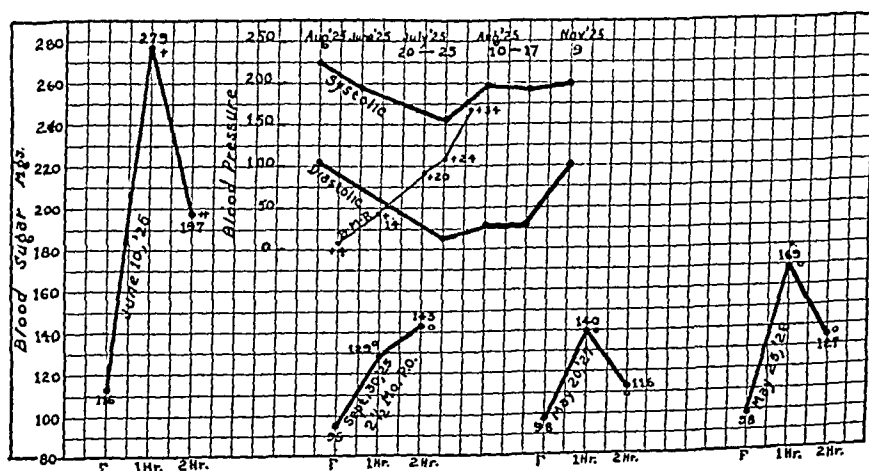


weeks. Sugar was found on routine urinalysis and the following morning her fasting blood sugar was 191 mgm. Reference to the chart will disclose the rapid return to a normal fasting level on a quantitative diabetic diet. The blood sugar curve the following day was certainly in the diabetic range. The basal rate at the same time was +32 per cent. Following removal of the thyroid, and on an unrestricted diet the two curves taken perhaps a little too early can certainly not be called diabetic, nor are they entirely normal. Subsequent curves six months or a year later might have been entirely normal. That this has been our experience in other cases, the charts will show.

The second patient, case H. T. (Chart 2), housewife, age 53, was first seen in September, 1923, because of symptoms referable to hypertension and mod-

CHART II

CASE—MRS. H. T. PATHOLOGICAL DIAGNOSIS—PARENCHYMATOUS HYPERPLASIA



erate obesity. No sugar in the urine was discovered at that time and the fasting blood sugar was 90 mgm. Reference to Chart 2 will show the blood sugar curves on her second admission two years later when she presented symptoms of nervousness, weakness, thirst and polyuria of two months' standing. No



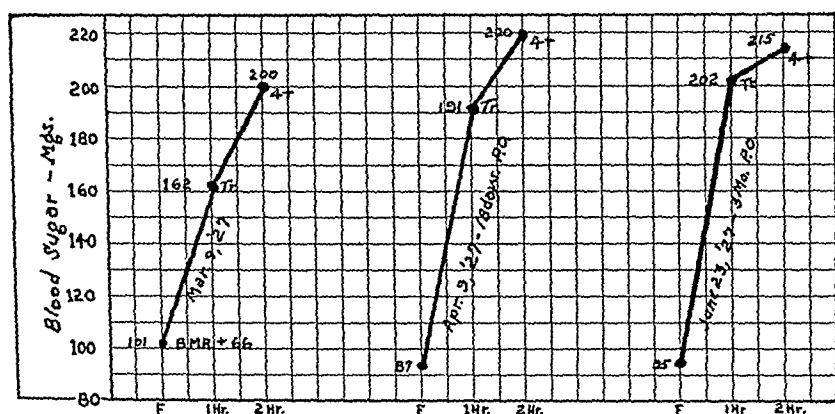
thyroid enlargement could be palpated and her symptoms were thought to be due to hypertension and a mild diabetes. A quantitative diabetic diet low in salt was started and the urine became sugar free immediately. Reference to the chart shows the falling diastolic blood pressure. Coincident with this a capillary pulse was first noticed and an increasing metabolic rate. Further search for a goiter was made and on stereoscopic chest films a substernal enlargement was seen which at operation proved to be a parenchymatous hyperplastic goiter. Two and a half months afterward on a diet unrestricted as to carbohydrate the blood sugar curve returned approximately to normal. Two years later it was entirely normal and a year later it was such as might be considered as representing a latent diabetes.

Wilder (4) mentions that there are a number of case reports in the literature which show return to normal tolerance following thyroidectomy. None of these, however, included blood sugar estimations after glucose meals. Gray (9) in 1923 reported a series of abnormal curves before and normal curves after removal of the thyroid. In Wilder's own case the patient had a fasting blood sugar of 271 mgm. and 60 gm. of sugar in the urine. One year following removal of 15 gm. of hyperplastic thyroid tissue, the curve was 110 mgm. fasting, 168 mgm. at one hour and 160 mgm. at two hours. He believes that on the basis of this evidence this patient had a latent diabetes.

Failure of the curve to return to normal following thyroidectomy is illustrated by case A. McL. (Chart 3). This patient, age 40, housewife,

### CHART III

CASE—MRS. A. McL. PATHOLOGICAL DIAGNOSIS—DIFFUSE PARENCHYMATOUS HYPERPLASIA

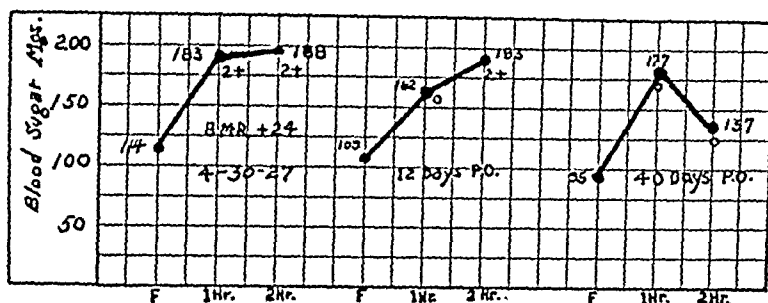


complained of nervousness, loss of weight and tachycardia for six months. No especial thirst or polyuria had been present. Both routine urines contained abundant sugar. Three months after removal of a parenchymatous hyperplastic goiter the curve showed even a higher second hour level than before operation. On the basis of experience in other cases one might have predicted a return to normal tolerance following operation. The results in this patient, however, demonstrate conclusively that one can not always predict the outcome.

A similar type of curve of lesser height is illustrated by case C. M. (Chart 4). This patient, a housewife, age 42, came with symptoms of

#### CHART IV

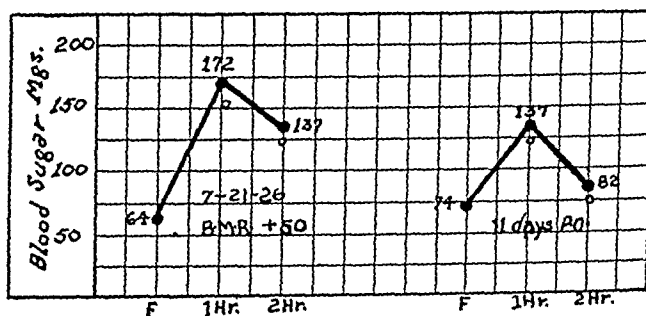
CASE—MRS. C. M. PATHOLOGICAL DIAGNOSIS—DIFFUSE ADENOMATOUS HYPERPLASIA WITH ADENOMATOSIS



nervousness and palpitation of ten months' duration without any of the classical symptoms of diabetes. Although the basal rate was only plus 24 per cent, the curve before operation is that of a potential diabetes. Forty days later it was in the borderline group quite similar to the final curve in case C. A. D. and the initial curve of case W. H. J. (Chart 5). The tendency for the second hour level to drop toward normal would seem to

#### CHART V

CASE—MRS. W. H. J. PATHOLOGICAL DIAGNOSIS—DIFFUSE PARENCHYMATOUS AND MODERATE ADENOMATOUS HYPERPLASIA



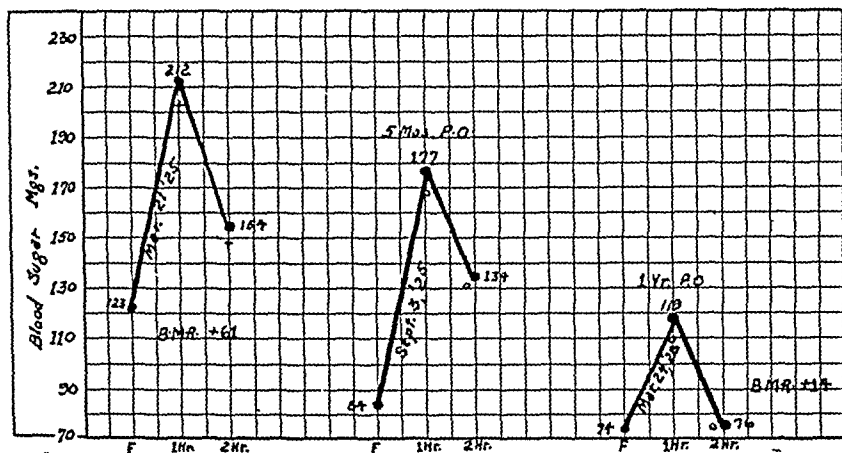
indicate that if a further curve had been taken six months or a year later it would have been entirely normal.

This contention is supported and illustrated quite clearly by the experience in case McC. (Chart 6) whose curve five months after operation is almost identical with that of case C. M. One year after operation it was entirely normal. This patient, age 40, a housewife, operated upon in 1921 for an adenomatous hyperplastic goiter, felt fine for a year; then her neck began to enlarge again and she lost weight. Her mother, age 60, has had diabetes for at least ten years. Here is our diabetic Anlage history clearly present in the mother, but the daughter with a hyperthyroidism in 1921 did not develop a diabetes, as the urines were sugar free at that time. The recurrent hyperthyroidism in 1925 had only a mild effect

on her tolerance despite the high metabolic rate of plus 61 per cent, and the final curve shows no evidence of a disturbed carbohydrate metabolism.

## CHART VI

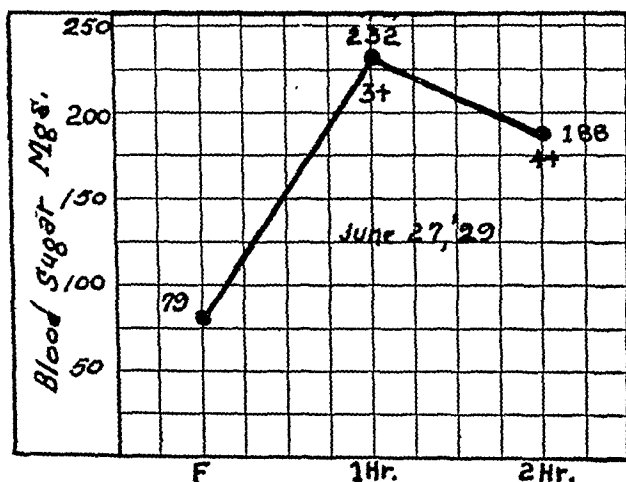
CASE—MRS. MCC. PATHOLOGICAL DIAGNOSIS—ADENOMATOUS HYPERPLASIA



A similar recurrent hyperthyroidism in case C. M. B. (Chart 7) is an illustration of disclosure of the diabetic Anlage in the father of a diabetic child who has been under our care for five years. This man, age 47, had a colloid adenoma removed in 1919, at which time no sugar was found in the urine. Again, in 1926, a double resection for a nodular adenomatous hyperplastic goiter was made. At this time the basal metabolism was

## CHART VII

CASE—C. M. B. "COLLOID ADENOMA" REMOVED APR. 4, 1918. NODULAR ADENOMATOUS HYPERPLASTIC COLLOID GOITER REMOVED DEC. 3, 1926. B. M. R. + 24

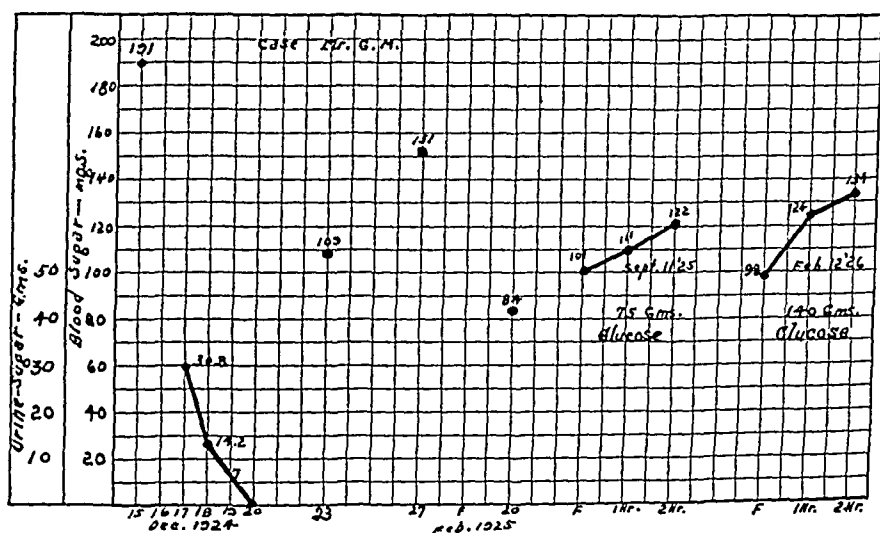


plus 24 per cent. Still no urinary sugar was present. In June, 1928, a trace of sugar was found, but none again until June, 1929, when a blood sugar curve gave the results shown on Chart 7. At that time no clinical

evidence of hyperthyroidism was present. The question arises as to whether this curve represents the residue of his old hyperthyroidism or evidence of a potential diabetes. Inasmuch as a hyperthyroidism ordinarily excites a latent diabetes and fans the flame, as it were, if this curve does represent a potential diabetes, why did not the two past instances of hyperthyroidism in his history precipitate it sufficiently to produce at least a glycosuria?

A third example of recurrent hyperthyroidism, not illustrated by a chart, bears a somewhat detailed report. A druggist, age 34, came in April, 1925, with symptoms of thirst and polyuria of a month's duration. A bilateral ligation for an exophthalmic goiter had been made elsewhere at age 22. He does not recall that anything was said about sugar in the urine at that time. Five years ago, at age 29, he was examined by a good internist who found sugar in the urine and obtained a blood sugar curve which the patient was told was normal and probably related to the goiter. Subsequent to this, in our records, the urine was negative for sugar. He had never been obese and there was no history of diabetes in the family. He

CHART VIII



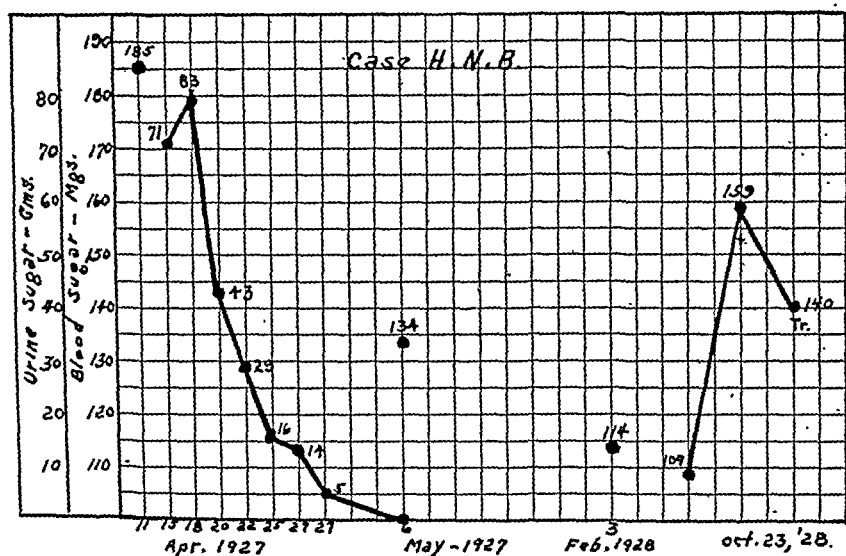
had, however, previous to the onset of the frank diabetes, eaten excessively of candy for four months, before this having been a heavy consumer of alcoholics. Examination revealed extreme emaciation, marked exophthalmos, tremor and sweating, and a toxic type of heart action. The basal rate was plus 36 per cent and the blood sugar 210 mgm. Seventy-five units of insulin daily was necessary to prepare him for operation. Subsequent to operation (pathological report: diffuse adenomatous and parenchymatous hyperplasia) his insulin dose was reduced to 40 units and his weight raised from 117 to 145 pounds.

If a diabetic Anlage is a prerequisite in every case of diabetes, why did not his hyperthyroidism at age 22 precipitate it? Was his glycosuria eight years later really a benign type? Is it possible that the most recent

hyperthyroidism at age 34 was really a more severe form and did the excessive carbohydrate intake, as suggested by John, produce irreversible changes in the islands of Langerhans?

The blood sugar curves of two patients with true diabetes, but without hyperthyroidism, are shown on Charts 8 and 9. The first patient, a laborer, age 44, without a history of diabetes in the family, had been tired for six months and had had thirst and polyuria for two months. He had lost in weight from 234 to 213 pounds in two months. He was still excessively overweight, being 5 feet 9½ inches tall. No doubt that a true diabetes

CHART IX



was present can arise from inspection of the chart, showing the initial blood sugar and the gradually decreasing glycosuria. Use of a quantitative diet for ten months and reduction of his weight to normal apparently had the effect of restoring a practically normal tolerance, at least as far as a blood sugar curve is concerned. Comparison of this curve with the second curve on Chart 1 reveals the fact that they are practically identical. Furthermore, undoubtedly were this patient with a restored tolerance subjected again to excessive food intake, obesity, infection, or a hyperthyroidism, a return of his diabetes would occur.

The second patient, Chart 9, a druggist, age 32, was also overweight approximately 30 pounds previous to the onset of his diabetes. The onset, moreover, dated from a period of financial worry. An uncle had diabetes. Classical symptoms ushered in the diabetes. Reference to the chart shows a blood sugar of 185 mgm. and, after a quantitative diet was started, a glycosuria of 81 gm. Without insulin he was desugarized in a month's time, and ten months later, maintaining his weight and a normal blood sugar on a diet of C-235, P-91 and F-98, he asked that a blood sugar curve

be plotted. Compare the result of this with the final curves on Charts 1 and 2 and mark the similarity.

Return of the tolerance to normal after institution of proper treatment in diabetes is, of course, not rare, as many cases of such have been reported in the past. Details of the above cited cases were given simply as a means of comparing the curves of diabetic patients without hyperthyroidism with those complicated with thyrotoxicosis.

We definitely know that a diabetic Anlage is present in both of these last mentioned patients. Have we any right to say from the evidence presented that a diabetic Anlage of mild degree does not also exist in the first two patients discussed?

The blood sugar estimations in this work were all made by the Shaffer Hartman method as modified by Haskins and Holbrook (10). The urine tests for sugar were made using the Benedict's qualitative reagent. The amount of glucose given the patients was 1.7 gm. per kgm. of body weight.

From the evidence obtained from the study of this small group of selected cases it should be evident that no conclusions may be drawn except that the diagnosis of diabetes in the presence of hyperthyroidism is not an easy or a settled problem. It is our opinion, however, that following thyroidectomy failure of the curve to return to normal after a sufficiently long time is indicative of the presence of a mild diabetes. For the time being at least, and until more is understood regarding this question, these patients will be treated as borderline diabetics and their blood sugar curves studied at least once a year.

#### SUMMARY

1. The literature regarding the problem of combined diabetes and hyperthyroidism is discussed.

2. A brief resume is given of the results in 24 thyroidectomized diabetic patients in connection with the pathological diagnosis.

3. The blood sugar curves before and after thyroidectomy in 7 patients with potential diabetes are presented with charts.

4. The blood sugar curves following dietetic treatment of two diabetic patients without hyperthyroidism are compared with the post-operative curves of the previous group.

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# CO-EXISTENT DIABETES MELLITUS AND DIABETES INSIPIDUS WITH CASE REPORT

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On both theoretical and physiological grounds one would expect to find but few cases of diabetes mellitus and diabetes insipidus associated. A search of the literature reveals reports of but three cases. Surely others have been observed or existed, but I have been unable to find reference to them.

Gibson, Magers and Dulaney (1) report a case in a man, aged 69, and refer to a case reported by Lanter and Hiller (2) in which the highest blood sugar was 128. Steel (3) reports a case in a boy, aged 14. There are certain disturbing features about all of the above cases. That of Gibson et al showed marked fluctuations of urine output and sugar tolerance. The case of Lanter and Hiller showed a maximum blood sugar of only 128 mgm. Steel's case followed an encephalitis and likewise showed rather marked variations in sugar tolerance (4). In other words, there seems to be no continuity and uniformity of the progress of these cases, which fact raises the question as to whether or not they represent true or transitory metabolic imbalances.

From the literature, one gets a confused idea of the etiology of diabetes insipidus. Some writers think of it as a hyper-pituitarism, while others think of it as a hypopituitarism. At the same time one finds references that speak in terms of a dyspituitarism. Finally, some observers go beyond the pituitary and etiologically implicate the sympathetic nervous system. As with so many other conditions, the conclusion of the inquirer is that the entire truth is not yet known.

I wish to add to this chaos, a report of what appears to be a true case of diabetes mellitus associated with diabetes insipidus.

## CASE REPORT

Mr. C. R. W., aged 40, white male, was born in the United States. His complaints when first seen by me were vomiting, diarrhea and blurred vision. These symptoms had been present off and on for three weeks, during which time he had lost between 25 and 30 pounds in weight. He weighed 98 pounds on admission to Baylor Hospital and was 69¾ inches in height. His blood sugar on admission was 333 mgm. per 100 cc. of blood. His urinary sugar was not quantitated but there was a large amount. His urine was likewise heavily positive with diacetic acid and acetone. His blood pressure was 94/64; temperature, 97° F., and pulse, 84. His blood picture showed 9,800 white cells with 71 per cent polymorphonuclears, 21 per cent small lymphocytes, 7 per cent large lymphocytes, and 1 per cent each of large monocuclear leucocytes and transitional cells. His blood Wasserman and Kahn reactions were negative. His blood urea nitrogen was 10 mgm. per 100 cc. His phenolsulphonephthalein excretion was 58 per cent in two hours. The spinal fluid was normal in every respect.

*Family History:* A maternal grandmother had a severe case of diabetes, but died of la grippe. A maternal aunt died of diabetes mellitus at ten years of age. His father had a "nervousness or palsy" manifested as a twitching of the hands and feet. All of his father's brothers had the same condition. The patient has been bothered all of his life with the same trouble, though to a relatively mild degree.

*Past History:* As a child he had measles, mumps and scarlet fever, but no other notable illnesses. The first symptom noted relative to present illness was increased output of urine in December, 1922. The onset was very insidious. After about four months, however, he had reached a state in which he could not retain his urine longer than two hours. At this time, he was drinking inordinate quantities of water. The urine was examined but only for albumin. He lost ten pounds in weight and had a voracious appetite. Not until three months later was sugar found in the urine. He was advised to limit his diet. He became very nervous at this time, and remained about ten pounds under weight. He had several teeth removed, quit work and followed rigidly the diet outlined in his diabetic manual and remained sugar free. Although the total output of urine decreased during this time, the patient continued to void considerably more urine than normally. A few months later he became careless with diet and symptoms of weakness, cramps in the legs, disturbance in vision and easy fatigue with loss of weight developed. At this time, about two years after the onset of symptoms, he developed a cold. He noted at the time an output of from eight to nine gallons of urine in twenty-four hours. Insulin was started and given up to 20 units daily. Even with insulin and rigid dieting, he continued to void about 12,000 cc. of sugar-free urine each twenty-four hours. He remained sugar free for eight months. A few months later he had the remainder of his teeth removed. He changed his residence at this time and discontinued the insulin. Sugar reappeared in his urine. About three and a half years later, he noted he was voiding 12,000 to 16,000 cc. of urine daily with traces of sugar. He returned home (Texas) and recommenced insulin. He became sugar free but continued to void around 12,000 cc. of urine daily.

His progress from this point on varied about as described above until in February of this year when he developed a "spell of rheumatism." At this time he was drinking from six to seven gallons of water daily. He began to vomit and could retain nothing, he lost weight rapidly. He was first seen by me about three weeks after this upset.

*Physical Examination:* The patient appeared emaciated. Except for a slight edema of the feet and ankles, a careful physical examination revealed nothing of importance. He was promptly started on insulin and routine measures for the treatment of acidosis and quickly stopped vomiting.

#### COURSE

Diabetes insipidus was not suspected at all in the beginning. As soon as the patient's sugar metabolism was balanced, it was thought that his condition would immediately clear up. To my surprise, his urinary output steadily rose from about five liters to eighteen, with a perfectly negative urine. The specific gravity ranged from 1.002 to 1.003. Studies of his renal function were made and all constituents were found to be within normal limits. It was at this point that diabetes insipidus, associated with diabetes mellitus, was suspected.

Numerous tests were then instituted in order to study his response to the pituitary preparations. "Pitressin" was first used. The result was to the patient phenomenal. For the first time in several years he experienced sensations heretofore forgotten. His thirst disappeared, he had no tendency to void, his mouth became moist and his "bowels were enlivened."

Blood sugar and chloride determinations were made at intervals of 20 minutes following the first injection of pitressin. There was no significant variation of either metabolite throughout a three-hour observation.



"Pitocin" was next used. Blood sugar estimations were made at thirty-minute intervals following the injection. This pituitary extract likewise showed a very slight effect upon the blood sugar level; in fact, less than the pitressin. The subjective effect was not unlike that experienced when pitressin was given. The effect upon the patient's thirst and urinary output, however, was decidedly less than that produced by the pitressin. Next insulin and pitressin were given together. The blood sugar variations differed in no wise from those just described (see table for data).

Finally, "obstetrical pituitrin" was given. Whether the subjective sensation was a residual effect of the previously administered split substance or whether it was specifically a result of the pituitrin, the patient felt that this injection caused him to feel more normal than any of the previous injections. Consequently, he continued to use obstetrical pituitrin therapeutically with most satisfactory results, subjectively and objectively.

Strangely enough, a few days after the pituitary products had been started, the patient began having slight insulin reactions, although his diet and insulin had been unchanged for about ten days. His insulin was then reduced.

The reaction to the pituitary extracts were so sharp that it was thought that possibly some of the immediate effects at least might be a result of a circulatory congestion of the kidney. To test this possible effect, ephedrine sulphate in  $\frac{3}{8}$  grain doses was given every three hours. It has been shown that this substance actually causes renal congestion (5). During the twenty-four hours that the patient received ephedrine, his urinary output steadily rose and his familiar abnormal thirst returned.

It is notable that especially pitressin caused a marked retention of fluids. The patient, during the beginning of his observations, would frequently show a gain of as much as six pounds in one day. To illustrate this effect, he was allowed to recover from the effects of the pituitrin. A water test was then performed. In 4 hours following the ingestion of 1500 cc. of water, he voided 2,445 cc. About 12 hours later, he was again given 1500 cc. of water and immediately given 10 cu. mm. of pitressin. At the end of the 4 hours it was with difficulty that he voided 100 cc. of urine which had a specific gravity of 1.020. During this procedure, his feet and lower legs became markedly edematous.

Intradermal salt tests showed a rapid disappearance time, averaging about 25 minutes. The tests were made before the patient's water metabolism was balanced.

Before discharge from the hospital, the patient's sugar and water metabolism were balanced. He was discharged taking fourteen units of insulin before breakfast and eight units before supper. He was taking pituitrin (obstetrical) 10 cu. mm. t. i. d., midmorning, midafternoon and midnight. On this schedule, he was voiding from 1800 to 3000 cc. urine

daily and running a fasting morning sugar around 200 mgm. So many hypodermics being irksome, he was allowed to discontinue one pituitrin injection and advised to take this extract at noon and bedtime. Upon this regimen he has gained considerable strength and his weight has increased (in about four weeks) 30 pounds. After leaving the hospital, however, even with obstetrical pituitrin, three times daily, his urinary output increased. He has been advised to change to pitressin. He believes now that this substance has a more active and sustaining effect than the obstetrical pituitrin. He is at present taking two to three injections of ten cu. mm. of pitressin daily, midmorning and midafternoon and at bed time and is voiding from 2400 to 4000 cc. of urine each 24 hours. He has had to increase his insulin to 15 units twice a day. He is taking a diet of proteins, 70; fats, 175; carbohydrates, 125 gm. Detailed data are recorded in Table 1.

#### COMMENT

The etiology and pathological physiology of diabetes insipidus are not known, consequently there exists no unanimity of theory regarding it. One popular view is that diabetes insipidus is a result of deficient functioning of the posterior lobe of the pituitary body. Another is that it is a disturbance in the vasomotor tracts somewhere in the region of the hypothalamus. A third view combines these two hypotheses.

The glandular theory is inadequate, because it has been shown that diabetes insipidus can be produced in animals by traumatising the hypothalamic region without any demonstrable injury to the pituitary body (6). Equally difficult to reconcile, is the fact that in Simmond's disease, or pituitary cachexia, in which there is practically a complete atrophy of the pituitary body, there have not been recorded any symptoms to suggest diabetes insipidus. Indeed, the reverse is true (7).

Conflicting with the vasomotor view is the fact that pituitrin controls the symptoms of the disease. The effect of pituitrin seems largely metabolic and not mechanical.

The last theory correlates both the experimental and clinical data best. Sajous (8) describes two nerve paths which begin in the posterior or neural lobe of the pituitary and pass up via the infundibulum to the tuber cinereum. From here they course down the bulb, spinal cord and splanchnics to the kidneys and adrenals. He claimed that these pituitarorenal and adrenal nerves controlled renal circulation. Lepine (8) holds that lesions anywhere in this double tract that blocks the impulses through it to the kidney and adrenals cause passive dilatation of the renal vessels and polyuria or diabetes insipidus. Cushing (9) believes that the pituitary is involved through the influence affecting the nervous tracts passing from the spinal cord to the superior cervical sympathetic ganglion and posterior ganglionic fibres to the pituitary. In Royntree's opinion, the whole truth

is not known as yet. He feels, however, that the pituitary gland exercises some control over kidney function.

TABLE I  
DATA SHOWING DAILY PROGRESS OF PATIENT  
First Admission to Hospital

1929 Date Feb	Urine Vol cc	Sp Gr	Sugar	Diet			Weight Lbs	Bl Sugar Mgm	Insulin U	Remarks
				P	F	C				
16		1 009	pos				98	333	15	Patient vomiting Vomiting ceased Condition improved
17	3090	1 005	trace	24	55	58	98	83	10	
18	5500	1 004	neg	44	76	71		118 A M 154 P M 100 A M 100 P M	18	
19	4150	1 004	"	43	110	57		160 A M 173 A M	10	
20	6040	1 002	"	46	121	61	110½	200 A M		
21	6970	1 003	"	54	147	76	111½	148 A M	20	
22	7930	1 003	"	52	134	75	112		27	
23	15300	1 004	"	50	127	76	114		27	
24	12450	1 002	"	60	157	86	115½		27	
25	14940	1 003	"	65	170	85	121	111 A M	15	
26	13085	1 002	"	65	178	85	120	129	27	
27	15690	1 002	"	65	179	85	126		27	
28	18320	1 003	"	65	181	85	127		27	
Mar 1	8710	1 004	"	65	181	87	127½	167	27	Pitressin, 10 m at 2 P M *
2	10200	1 001	"	65	181	87	126½		37	Pitressin, 10 m with 10 units of insulin at 2 P M †
3	7300	1 005	"	65	181	85	124½		27	Pitressin, 1 cc at 2 P M
4	11418	1 005	"	64	171	77	125½		27	Pitocin, 12 m at 2 P M ‡
5	11280	1 005	"	65	181	85	124		22	Insulin reaction in A M and P M
6	6840	1 007	"	65	181	85	118½	133	10	Pituitrin (0), 12 m, at 2 P M §
7	17110	1 007	0 5%	65	181	85	111	182	10	Pituitrin (0), 10 m, t i d
8	6000	1 009	0 6%	65	181	85	111½	286	15	Pituitrin (0), 10 m, t i d
9	5150	1 008	0 5%	70	175	100	109½	200	15	Pituitrin (0), 10 m, t i d
10	1760	1 008	trace	70	175	100	109½		15	Pituitrin (0), 10 m, t i d
11	3000	1 009	"				110	235	23	Pituitrin (0), 10 m, t i d
12							111½	200	23	Discharged

Second Admission to Hospital

1929 Date Mar	Urine Vol cc	Sp Gr	Sugar	Diet			Weight Lbs	Bl Sugar Mgm	Insulin U	Remarks
				P	F	C				
25	1220	1 006	0 6%	70	175	125		211	27	Pituitrin (0), 10 cu mm t i d
26	2780	1 015	1 2%	70	175	125	119¾	222	27	Pituitrin (0), 10 cu mm t i d
27	3400	1 010	0 6%	70	175	125	120½	235	27	Pituitrin (0), 10 cu mm t i d
28	7380	1 005	trace	70	175	125		222 A M 200 P M	27	Pituitrin discontinued
29	7120	1 007	"	70	175	125	123½		27	Pituitrin (0), b d
30	7406	1 010	neg	70	175	125	124	235	30	Pituitrin (0), 8 cu mm t i d
31	3100	1 010	"	70	175	125	122½		30	Pituitrin (0), 8 cu mm t i d
April 1							120½	182	30	Discharged

\*Blood sugar reading before and each 20 minutes following the pitressin were: 118, 125, 118, 105, and 125. Blood chloride readings at the same intervals were: 459, 457, 475, 469, and 464 (Mgm per 100 cc. of blood)

†Blood sugar readings before and each 30 minutes following pitressin and insulin were: 105, 118, 133, 105

‡Blood sugar readings before and each 30 minutes following pitocin were: 67, 105 and 118

§Blood sugar readings before and each 30 minutes following obstetrical pituitrin were: 100, 133, 125 and 133

Bourquin's (10) recent experimental work on diabetes insipidus is interesting, but does not help a great deal toward clearing away the obscurity surrounding the pathogenesis of this disease. Her work does certainly implicate the central nervous system, but in just what way remains to be determined.

One is impressed with the increasing importance of the relationship of the sympathetic nervous system with the endocrine system. It is difficult to separate the two systems functionally. When this functional relationship has been sufficiently examined, doubtless many apparent incongruities will be made clear and many gaps of knowledge filled.

Just why the patient reported in this paper should have diabetes mellitus associated with diabetes insipidus, I cannot say. The temptation to spin a theory of causal relationships is withstood, since, as Rowntree (11) has said, the field of internal secretion is already famous for few facts and many fancies.

From an endocrine viewpoint, I can see no reason for the co-existence of the two diseases. With an overactive pituitary gland one may expect and does find a secondary effect on other glands, notably the thyroid and pancreas (12). But in the case of diabetes insipidus, where the pituitary disturbance is not thoroughly understood—indeed may not even exist as a primary hypofunction or dysfunction, it is probably safer to consider the co-existence of diabetes insipidus and diabetes mellitus as purely a rare though fortuitous circumstance.

I wish to suggest and emphasize one point. Symptoms of diabetes insipidus, so generally considered to be a result of dehydration, are probably in large measure a result of pituitary-sympathetic nervous system disturbance. I refer to the dryness of the mouth, the dead feeling of the intestines, dry skin, etc.

In the case herein reported, the patient's own observation of the almost *immediate* disappearance of the "dead sensation" of the bowels, return of the moisture in his mouth, etc., following the administration of pituitrin, is, I think, significant. It is more probable that the constipation, dead sensation, as well as other symptoms, are a result of sympathetic nervous system disturbance with associated pituitary dysfunction; in other words, a primary instead of a secondary effect.

#### SUMMARY

A case of co-existent diabetes mellitus and diabetes insipidus in which different pituitary extracts were used is reported in detail. The observations suggest that pituitrin and insulin are not as physiologically antagonistic as ordinarily believed, at least in the presence of diabetes mellitus and diabetes insipidus.

Pitressin seemed to exert more of a blood sugar raising effect than did pitocin, and about the same as obstetrical pituitrin. Pitressin was the most active in controlling the symptoms of diabetes insipidus.

It is suggested that many of the symptoms of diabetes insipidus, such as constipation, dryness of the mouth, skin, etc., are a primary result of a sympathetic-pituitary disturbance and not a secondary result of dehydration.

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# Book Reviews

LA NEUROCRINIE HYPOPHYSIAIRE. ETUDE HISTOPHYSIOLOGIQUE DU COMPLEXE TUBERO-INFUNDIBULO-PITUITAIRE. R. Collin. 1928. Arch. de morph. génér. et expér. 28: G. Doin, Paris. Pp. 112.

Reviewed in Endokrinologie, 2: 399. 1928.

THE GLANDS OF DESTINY: A STUDY OF THE PERSONALITY. Ivo Geikie Cobb, 1928. Macmillan, N. Y. Pp. 302.

The book is roughly a mixture of "Why We Behave like Human Beings" and "Glands Regulating Personality." It is not so good as Dorsey and is better than Berman.

TRAITEMENT DU GOUTTE SIMPLE. Bargeat. 1927. Legrand, Paris.

Reviewed in Presse méd. 36: 1032. 1928.

KONSTITUTION UND INNERE SEKRETION. L. Borchardt. 1926. Carl Marholds, Halle a. S. Pp. 56.

Reviewed in Schweiz. med. Wehnschr. 58: 811. 1928.

HORMONE UND STOFFWECHSEL. W. Raab. 1926. Dr. F. P. Datterer & Cie. Friesing-München. Pp. 195.

Reviewed in Schweiz. med. Wehnschr. 58: 811. 1928.

DIE INNERE SEKRETION IM LICHT DER MORPHOLOGISCHEN FORSCHUNG. Berblinger. 1928. Gustav Fischer, Jena. Pp. 30.

Reviewed in Schweiz. med. Wehnschr. 58: 811. 1928.

ABHÄNGIGKEIT DER WACHSTUMSSTÖRUNGEN UND KNOCHENERKRANKUNGEN VON STÖRUNGEN DER INNEREN SEKRETION. O. Maas. 1926. Carl Marholds. Halle a. S. Pp. 55.

Reviewed in Schweiz. med. Wehnschr. 58: 811. 1928.

# Abstract Department

**Contraction of the spleen and changes in the splenic blood produced by adrenin injection in animals** (Contraction de la rate provoquée par l'injection d'adrénaline et comportement du sang splénique chez les animaux). Borysiewicz, A., *Compt. rend. Soc. de biol.* **99**: 931. 1928.

Blood from the splenic vein of dogs was examined. In 60% of cases, adrenin produced a splenic contraction which increased the red blood cell count markedly.—J. C. D.

**Action of adrenin on calcium, potassium, and metabolic rate in normal cases and those with thyroid disorders** (Action de l'adrénaline sur la dépense calorique, la calcémie et la potassémie chez l'homme normal ou atteint de troubles thyroïdiens). Castex, M. R. and M. Schteingart, *Compt. rend. Soc. de biol.* **99**: 1649. 1928.

Injection of adrenin produced an equal rise in basal metabolism in both normal and sick individuals. No relation between this rise and variations in calcium and potassium could be observed.—J. C. D.

**Adrenal syndrome in yellow fever** (Syndrome surrénal dans la fièvre jaune). Chagas, E., *Compt. rend. Soc. de biol.* **99**: 1664. 1928.

The typical syndrome of adrenal insufficiency appeared in 10 to 15% of the cases on about the tenth day.—J. C. D.

**The influence of desiccated suprarenal cortex and medulla on the growth and maturity of young rats.** Chidester, F. E., A. G. Eaton and G. P. Thompson, *Am. J. Physiol.* **88**: 193. 1929.

Growth of young rats is retarded by 0.5 gram of either desiccated suprarenal medulla or cortex and is retarded, especially at first, by desiccated suprarenal cortex. Young female rats fed 0.5 gram of desiccated suprarenal cortex (as shown by earlier litters) reach sexual maturity sooner than controls or those fed on 0.5 gram desiccated suprarenal medulla daily. Males were not tested independently with older females so that it is not certain whether or not they reached sexual maturity earlier than the females of their own litter.—Authors' summary.

**Effect of adrenal tissue on lecithin** (Action du tissu surrénal sur la lécithine). daCruz, A., *Compt. rend. Soc. de biol.* **99**: 1530. 1928.

Fresh adrenal and liver tissue from guinea pigs was incubated at 37° in test tubes for 24 hours while in contact with lecithin. Both tissues split lecithin. The liver tissue is only slightly more active than the adrenal. Cholesterol added to the solutions intensifies the reaction.—J. C. D.

**Oestrous cycle in adrenalectomized rats** (Le cycle oestral du rat normal et décapsulé). Del Castillo, E. B., *Compt. rend. Soc. de biol.* **99**: 1403. 1929.

The operation did not interfere with the cycle nor with the age of opening of the vagina.—J. C. D.

**The influence of suprarenal cortex and medulla on the growth and maturity of young (white leghorn) chicks.** Eaton, A. G., W. M. Insko, G. P. Thompson and F. E. Chidester, *Am. J. Physiol.* **88**: 190. 1929.

The influence of adrenal cortex and medulla on the growth and maturity of young white leghorn chicks is discussed. Chicks fed desiccated suprarenal medulla grew almost the same as the controls for the first three weeks. After

that time their growth was less rapid than the controls. Chicks fed desiccated suprarenal cortex grew much more slowly at first than the controls. But by the end of the first eight weeks they began to grow more rapidly, and toward the end of the experiment almost equaled the controls in weight. If the weights of the testes are any indication of maturity, males receiving desiccated suprarenal cortex were more mature than either of the other lots, and those receiving desiccated medulla were less mature than those of the other lots. The average weight of the testes of the lot receiving desiccated suprarenal cortex was 0.2171 gram; the average of those receiving medulla was 0.1242 gram; while that of the controls was 0.2000 gram.—Authors' summary.

**The diagnosis of adrenal tumors.** Gibson, T. E., California & Western Med. 26: 201. 1927.

A consideration of adrenal involvement is often forgotten in the diagnosis of abdominal conditions. Adrenal tumors give rise to three distinct clinical syndromes: (1) the genito-suprarenal syndrome, due to cortical tumors (carcinoma); (2) Hutchison syndrome, and (3) Pepper syndrome, both due to medullary tumors (neurocytoma). A knowledge of these renders the diagnosis of adrenal tumors comparatively easy, not only in differentiating them from other tumors, but also in distinguishing between the cortical and medullary neoplasms of the adrenals themselves. Unfortunately, most text books do not clearly portray these syndromes and the literature is fragmentary. Cortical carcinoma arises probably on the basis of cortical hyperplasia or adenoma formation. These benign precursors of carcinoma give rise to the same clinical picture of cortical adrenal tumor as does carcinoma itself. Neurocytoma is the common tumor of the medulla. It is often called "sarcoma" in the literature. Probably the vast majority of the retroperitoneal sarcomas of infancy arise in the adrenal medulla.—I. B.

**Interrenin, the hormone of the suprarenal cortex (Interrenin, das Hormon der Nebennierenrinde [Vorläufige Mitteilung]).** Goldzieher, M., Klin. Wchnschr. 7: 1124. 1928.

The author believes he has isolated a hormone from the suprarenal cortex, which he calls "interrenin." The method of isolation is similar to that employed for insulin by Allen, Piper, Kimball and Murlin. The active principle is a white amorphous powder soluble in alcohol and in dilute acids and insoluble in distilled water, weak alkalies, ether and chloroform. The physiological properties are briefly as follows: Intravenous injection produces a fall in blood pressure acting as an antagonist to adrenalin. Injection of proportional doses of adrenalin and interrenin produces no effect on either the blood pressure or pulse rate. Interrenin produces a decrease in the blood lipoids, at times as much as 50 per cent diminution being obtainable in cholesterol and lipid phosphorus. The maximum point is generally reached in an hour but at times the effect lasts longer, reaching the peak in two hours and beginning to decline after four hours. The material injected into rats which had undergone double adrenalectomy produced a prolongation of life for several months. Control animals without interrenin died within 14 days after a double adrenalectomy.—M. B. G.

**The cephalic metastases of suprarenal blastomata in children.** Grieg, D. M., Edinburgh M. J. 36: 25. 1929.

The case was that of an eleven-months-old boy in which extensive exostoses occurred on the frontal and other bones near the orbit. These changes are shown in photographs.—J. C. D.

**Variations in blood pressure in the head. Separation of the neuro-vascular from adrenal secretory reflex (Les variations de la pression artérielle dans la circulation céphalique. Déclenchement des réflexes neuro-vasculaires et adrénalino-sécrétoires).** Heymans, C., Compt. rend. Soc. de biol. 99: 1239. 1929.

Using the method of vascular anastomosis between dogs, the authors find that compensatory changes in blood pressure in the trunk rise from the stimu-



lus of low or high blood pressure acting on the carotid sinus and so through the sympathetic, on vascular tonus directly and also indirectly by producing a discharge from the adrenals.—J. C. D.

**Adenoma of the adrenal cortex.** Hicks, J. B., *New England J. Med.* **199**: 1140. 1928.

The tumor occurred in a woman forty-eight years old and was successfully removed. The patient showed diffuse yellow pigmentation, an unusual sign in this condition.—J. C. D.

**Studies on the hyperglycemia following morphine injections: Rôle of the adrenals** (*Etudes sur l'hyperglycémie consécutive à l'injection de morphine. Rôle des surrénales*). Houssay, B. A., J. T. Lewis and E. A. Molinelli, *Compt. rend. Soc. de biol.* **99**: 1408. 1929.

From extensive studies on dogs, the authors conclude that the adrenals respond to morphine by an increased discharge of adrenin. The adrenals play an active but not essential part in morphine hyperglycemia. When the medulla is removed instead of the entire gland, morphine hyperglycemia is after a time as intense as though the glands were intact.—J. C. D.

**Formation of adrenaline-like substance in heart** (*Sur la formation dans le cœur d'une substance semblable à l'adrénaline par suite de l'excitation du nerf sympathique*). Lanz, A. B., *Arch. néerl. de physiol.* **13**: 423. 1928. *Abst., Physiol. Absts.* **13**: 637.

The substance formed in the frog's heart on sympathetic stimulation shows several of the reactions of adrenaline in addition to accelerating another heart (it is not given up to the perfused Ringer's solution without sympathetic stimulation). Thus on perfusion through the frog's hind limbs it produces vaso-dilatation in very weak concentration and vaso-constriction in higher concentration; the amount present in the perfusing fluid depends on the intensity of the sympathetic stimulation of the heart. A weak solution of glycine dilates the frog's aorta, but increases the constricting effect of the unknown substance, similarly to its activating influence on adrenaline. The unknown also inhibits the rhythmic contractions of the isolated frog's stomach. It is destroyed by boiling, and gives Russmann's adrenaline reaction with sulphanilic acid and mercuric chloride. It is therefore adrenaline itself.

**Intracardiac injection of epinephrine in a case of later postoperative embolism and heart failure.** Lutaud, P., *Bull. et Mem. de la Soc. des Chir. de Paris*, **20**: 874. 1928. *Abst., J. A. M. A.* **92**: 937.

Lutaud reports a case of embolism and heart failure in a woman, aged 28, 10 days after a successful laparotomy. Epinephrin was injected intracardially from 8 to 10 minutes after the heart had stopped functioning, and in one minute after the injection one could observe the oscillations of the needle left in the heart region. After 10 minutes of artificial respiration the heart sounds became regular, and the patient started to breathe. She recovered without any further complications.

**Suprarenal tumor with metastasis and optic neuritis.** Mandel, L., *Proc. Roy. Soc. Med.* **22**: 646. 1929. (Sec. Dis. Child.)

This is a report of a case of sarcoma of the left suprarenal body with metastases to the skull and elsewhere, occurring in a girl of six.—I. B.

**Changes in the arterial vaso vasorum in the rabbit following intravenous injections of adrenin** (*Modifications apportées par l'injection intraveineuse d'adrénaline à la circulation nourricière des parois artérielles du Lapin*). The early microscopic changes in adrenin arterio-sclerosis (*Les premières étapes histologiques de l'athérome adrénalinique expérimental*). Ravault, P. P. and C. Bouysset, *Compt. rend. Soc. de biol.* **99**: 828. 1928.

A study of the absorption of trypan blue injected intravenously shows that the intima and inner zone of the media in the arteries are nourished

from the blood in the lumen of the vessel, while the rest of the wall is supplied by the vasa vasorum. The same method shows that following injection of adrenin, the vasa vasorum is constricted and, therefore, the blood supply of the external half of the media and that of the adventitia is interfered with. The initial permanent change in the walls of the vessels, as seen microscopically, is an oedema of the middle portion of the tunica media followed by deposition of calcium.—J. C. D.

**On the effect of insulin administration upon the epinephrine content of the suprarenal body on rabbits.** Saito, S., *Tohoku J. Exper. Med.* 12: 263. 1929.

When insulin was administered to rabbits in a dose sufficient to cause convulsions, the epinephrine content of the suprarenal gland, determined by the colorimetric method of Suto and Inouye (14 cases) and of Folin, Cannon and Denis, and the rabbit intestine segment method (15 cases) showed a diminution, except in case of glands protected by denervation. When the same dose of insulin was given, with glucose simultaneously in adequate amounts, the diminution did not take place in the epinephrine load in the suprarenal capsule with intact innervation.—R. G. H.

**Significance of the augmented epinephrine secretion after haemorrhage in dogs upon the simultaneous occurrence of hyperglycaemia.** Tachi, H. and S. Saito, *Tohoku J. Exper. Med.* 11: 218. 1928.

Adrenalin was administered intravenously to splachnotomized, unanaesthetized dogs at a constant rate corresponding to the rate of adrenin secretion following hemorrhage (as determined previously by the authors in experiments in which suprarenal vein blood collected from unanaesthetized dogs following partial exsanguination was assayed for its adrenin content). Infusion of adrenalin was quite regularly accompanied by the development of a marked hyperglycemia. The authors conclude that the increased adrenin output after haemorrhage is an important factor in producing the hyperglycemia which develops simultaneously.—R. M. Moore.

**Lesions of the adrenal in yellow fever (Lésions des surrénales dans la fièvre jaune).** Torres, C. M. and A. P. deAzevedo, *Compt. rend. Soc. de biol.* 99: 1673. 1928.

The usual damage as seen in infectious fevers appears. The intracellular, doubly refractile, acidophile granules are unusually abundant.—J. C. D.

**The action of adrenin and cholin on the blood pressure in decapsulated dogs (Action hémodynamique de l'adrénaline et de la choline chez les chiens surrénalectomisés).** Troilo, E., *Compt. rend. Soc. de biol.* 99: 1521. 1928.

The sympathetic system is more sensitive to adrenin and the vagal system less sensitive to choline after adrenalectomy.—J. C. D.

**Vagal function in adrenal insufficiency. Lack of vagal tonus (La fonction vagale dans l'insuffisance surrénale. Inexistence du tonus vagal).** Viale, G., *Compt. rend. Soc. de biol.* 99: 1522. 1928.

In dogs, decapsulization produces what may be considered a sympathetic hypertonus and a vagal hypotonus.—J. C. D.

**Discharge of choline into the blood after injection of adrenin (Décharge de choline dans le sang après injection d'adrénaline).** Viale, G. and T. Combes, *Compt. rend. Soc. de biol.* 99: 1524. 1928.

The choline in the blood of the adrenal vein of dogs rises about 50% five or ten minutes after injection of adrenin.

**Pneumin.** A respiratory autocoid from the adrenal cortex discharged into the circulation via the lymphatics. Vincent, S. and J. H. Thompson, *J. Physiol.* 67: 3. 1929.

Respiratory failure in decerebrate cats followed extirpation of both adrenals, ligation of the blood supply thereto, damage to the lymphatics behind the glands, or interruption of the thoracic ducts. Intravenous injection of fresh adrenal extract restored respiration while adrenalin did not. Destruction of all tissue connections with the adrenals except the lymphatics and the arterial supply did not affect respiration. Cautey of the medulla was without effect. The authors conclude that an incretion that is essential to normal respiration passes via the lymphatics. The name **pneumin** is suggested.

—C. I. R.

**Virilism (masculinity) in a case of adenoma of the suprarenal cortex.** Winkel, M., *Deutsche Arch. f. Klin. Med.* 159: 1. 1928.

A report (with photographs) on a woman, aged 36 years, who had, over a period of 11 years, gradually developed the clinical syndrome of virilismus suprarenalis, namely, amenorrhea since the age of 26, obesity, heterosexual hypertrichosis, marked atrophy of uterus and ovaries, and hypertrophy of the clitoris. Such cases are rare but are recognized as due to hyperplasia (usually, tumorous) of the suprarenal cortex. In addition Winkel's subject presented symptoms suggestive of hyperactivity of the suprarenal medulla, namely, hypertension (215-225 mm. Hg., systolic) with "blue red" cheeks, renal diabetes (glycosuria unrelated to dietary intake, and refractory to insulin), polyglobulism, and relative polymorphonuclear leucocytosis. The refractory reaction to insulin was interpreted as due to an excessive production of adrenalin. Suggestive findings by palpation and roentgenograms justified a diagnosis of right-sided adrenal tumor, which was corroborated at operation and proved to be an adenoma of the suprarenal cortex. It was readily removed but the patient died two days later. Autopsy revealed atrophy of both adrenals, ovaries and thyroid. The pancreas and hypophysis were normal.—H. L.

**Carotid body tumor.** Sellors, T. H., *Proc. Roy. Soc. Med.* 22: 705. 1929. (Sec. of Surgery.)

This is a description of a case in a man aged 54 years. Swelling was first noticed in the neck following a dental abscess. A definite mass of enlarged glands at the angle of the jaw was noticed, and as the tonsils were manifestly septic they were removed. Hodgkin's disease was suspected but no further evidence of it could be found. The mass increased slowly in size and the patient lost weight. Tumor of the carotid body was confirmed by operation.—I. B.

**A hormone mechanism for gall-bladder contraction and evacuation.** Ivy, A. C. and E. Oldberg, *Am. J. Physiol.* 86: 599. 1928.

An extract of the upper intestinal mucosa has been shown on intravenous injection to cause contraction and evacuation of the gall-bladder. The extract is free of vaso-dilatin and has no objective toxic effect on unanesthetized dogs. Cross-circulation experiments show that when acid is injected into the duodenum, something gets into the blood which causes the gall-bladder to contract. It is thought that this observation proves a hormone mechanism for gall-bladder contraction and evacuation. It is pointed out that other mechanisms may be concerned in gall-bladder evacuation. The terms "cholecystokin" has been proposed as a name for the hormone and the active substance in intestinal extracts, which causes the gall-bladder to contract and evacuate. The amount of pressure that results from the contraction of the gall-bladder under the influence of "cholecystokin" is for one injection a maximum of 11.5 cm. of bile pressure and a minimum of 1.0 cm., and for a series of injections an average of 10.0 cm. and a maximum of 22.5 cm. in anesthetized dogs; and in unanesthetized dogs for a series of injections it is an average of 20.0 cm. of bile and a maximum of 24.0 cm. of bile. The average duration of the contraction for a single dose is 15 minutes. Following a series of doses the gall-bladder relaxes in from 30 to 60 minutes. The injection of the following

substances into the duodenum of the dog caused the gall-bladder to contract with the animal under light barbital-ether anesthesia: 15 to 40 cc. of N/10 HCl, 30 cc. of butter, digested egg-yolk, cream of olive oil, 0.5% butyric acid, and 5% soap solution. Undigested olive oil, egg-yolk and cream were ineffectual. Spontaneous rhythmic contractions of the gall-bladder were observed to occur from 2 to 4 times a minute. A small dose of "cholecystokinin" would usually increase their amplitude to as much as 3 cm. of bile pressure; a large dose would usually cause them to disappear at the height of the contraction, but they would reappear some time during the period of relaxation. If they were not present prior to the injection, they would frequently appear during the latter part of the period of relaxation. It has been observed that the hepatic ducts are injected with Ipiodol during the contraction of the gall-bladder, the injection of the ducts being due, it is thought, to increased (abnormal?) tone of the duodenum or sphincter of Oddi.—Authors' Abst.

**Endocrine disturbances in infant and adolescent psychopathies. Their relation to hereditary syphilis (Les troubles endocriniens dans les psychopathies de l'enfance et de l'adolescence. Leurs rapports avec l'heredo syphilis).** Drouet and Hamel, *Rev. franç. d'endocrinol.* 7: 1. 1929.

Examination of some 108 known psychopathies showed certain syphilitic ancestry for 92 or about 90%. Improvements in some cases were produced with thyroid and acetylarsan.—B. C.

**Tinnitus aurium; its incidence in endocrine disorders.** Drury, D. W., J. A. M. A. 91: 1508. 1928. Abst., J. A. M. A.

Analysis made of 1,000 cases at the Evans Memorial, 585 of which were demonstrably endocrine, showed an incidence of tinnitus in 35.6% of the endocrine cases and 32.7% in the non-endocrine cases. Further analysis of the non-endocrine group showed an appreciable percentage of diseases in which tinnitus is a characteristic or frequent symptom. It is concluded that while tinnitus aurium is not a characteristic symptom of ductless glandular affections, it is encountered equally often in hypofunction of the endocrine glands.

**An investigation of the effect of glandular therapy on the intelligence quotient.** Fox, Edna J., *Ment. Hyg.* 12: 90. 1929.

The article attempts to present some definite material on the relation of glandular therapy to intelligence in terms of I. Q. One hundred and eighty-two patients were diagnosed as suffering from some definite endocrine dysfunction involving one or more glands and in each case some glandular therapy was prescribed. The majority of subjects ranged in age from 3 to 16 years. One hundred and one were diagnosed as hypothyroid, 3 as hyperthyroid, 23 hypopituitary, 2 hyperpituitary, 3 thyro-pituitary and the remaining 50 as pluriglandular. The intelligence quotient for each individual was established by means of the Terman Revision of the Binet-Simon Intelligence Test, the average I. Q. being 74, the lowest 30 and the highest 115. The hyperthyroid cases were the most intelligent, the hyperpituitary the least. In 22 cases a second and third psychological rating was secured after from 4 months to 2 years of glandular treatment. Ten of these rated lower and 12 higher than on the first test, the greatest gain for any individual being 11 points. The pluriglandular group showed the greatest gain. While the subjects profited physically and emotionally from the glandular treatment, there was no perceptible variation in their intelligence quotients.—Gertrude Hoskins.

**Detection and action of a circulatory hormone (Nachweis und Wirkung eines Kreislaufhormons).** Frey, E. K. and H. Kraut, *München. med. Wchnschr.* 75: 763. 1928.

The authors give a summary of their work up to the present time on what they term the circulatory hormone. It was first noted that the intravenous injection of human or animal urine regularly produced lowering of the blood pressure, an increase in the amplitude of the pulse and usually an increase in

the heart rate. These effects last from one-half minute to ten minutes. The substance has some similarity to histamine, but the authors believe it is a different compound. Histamine produces an increase of blood pressure in rabbits and an increase in the liver volume of dogs; two effects which are not obtained with their material. The hormone becomes inactive when mixed with blood. This inactivity, however, is due not to destruction, but to a combination with the blood. The combination can be again broken down by treatment with papain. The kidneys have the ability to activate the hormone when it is inactive.—Ralph H. Major.

**The influence of endocrine secretions and of alkaloids on the permeability of animal membranes** (*Ueber den Einfluss von Inkreten und vegetative Giften auf die Permeabilität tierischer Membranen*). Gellhorn, E. and Hilde Gellhorn, Arch. f. d. ges. Physiol. **221**: 247. 1928.

Permeability of muscle and skin membranes to sugar is increased by adrenine 1:1,000,000, by thyroxine (from 1:10,000 to 1:1,000,000), and also by insulin.—A. T. C.

**Muscle chemistry under the influence of endocrine secretion and of poisons** (*Der Muskelchemismus unter dem Einfluss von Inkreten und Giften*). Handovsky, H., Arch. f. d. ges. Physiol. **220**: 782. 1928.

Lactic acid and carbohydrate content of muscle depend, amongst other factors, on the adrenal secretions (especially in male animals) and the testes. —A. T. C.

**Endocrine factors in dementia praecox.** Hoskins, R. G., New England J. Med. **200**: 368. 1929.

Fifty-three outstanding papers in the literature are reviewed. The survey leaves one with the overwhelming impression that scarcely a single detail has been satisfactorily established. Only a beginning has been made in determining the significance of the possible endocrine factors in dementia praecox. That the sex life and habitus are frequently abnormal is fairly definitely established. This correlates with the fact that the primary sex glands very commonly give histological evidence of degenerative changes or of aplastic development. The fact that similar changes are found in states other than dementia praecox signifies merely that in these conditions, too, gonad failure may play a rôle. A similar comment may be made on the degenerative conditions reported in the adrenals, the pituitary and the thyroid. The fact that such conditions are not found in all cases of schizophrenia would seem merely to indicate that endocrine deficiency is not the sole cause of the disease, though it may well be an important contributory factor. To determine the matter we must have many more exhaustive diagnostic studies. These must be rounded out by equally exacting therapeutic tests. The fact that more than one-sixth of all hospital beds in the United States are devoted to victims of dementia praecox constitutes this disorder the most insistent challenge to American medicine. In meeting this challenge much more work must be devoted to a determination of the part played by endocrine factors in its causation and of the possible value of endocrine substance in its treatment.

—Author's Abst.

**The endocrinology of tuberculosis.** Obermer, E., Proc. Roy. Soc. Med. **21**: 329. 1928.

The author suggests that the endocrines hold the key position in the mechanism of resistance to infection. In man the glands of internal secretion are divided into two counterbalancing groups. It is the function of the "katabolic" group—or glands of emergency—to react to acute infections. It is the function of the "anabolic" group—or glands of conservation of energy—to counterbalance the prolonged overaction of the katabolic group in chronic infections. In chronic pulmonary tuberculosis improvement is dependent on the predominance of the anabolic group. Clinical and biochemical evidence to this effect is offered. The individual ductless glands are discussed with a

view to summarizing the known tests for detecting their functional variations during life. The classification of cases of pulmonary tuberculosis according to the mode of endocrine reaction rather than to the extent of lung invasion is advocated. Emphasis is laid on the necessity for research into the heredity and environmental factors which lead to injury of the ductless glands, and hence lowered resistance to disease.—I. B.

*Clinical study of mongolian idiocy* (Zur klinik der Mongoloiden Idiotie). Orel, H., Ztschr. f. Kinderh. 44: 448. 1927.

This study is based upon clinical observations of 95 patients, of whom 54 were males and 41 females. Only 14 were above 10 years of age. The author feels that the incidence of Mongolian idiocy in Vienna is not very great, as in a survey of two institutions housing 600 mentally defective children, only 5 were Mongolian idiots, an incidence of less than 1%. There has been an increase in the incidence of this condition in the past few years. It has been found in all European races and also in Negroes and in Chinese. The patient was the product of the mother's last pregnancy in 51 cases (86%) and of the only pregnancy in 11 instances (12%). In 59% of the cases, the age of the parents was between 35 and 49 years. A familial history of some mental delinquency was found in 14 families. The condition of the thyroid in the patients under study revealed no abnormal findings. The cardiac condition was generally normal. There was an incurving of the little finger in the majority of children. The delinquencies found were in mentality, walking and talking. There seemed to be a love of music. The author refers to the slit between the anterior and middle clinoid processes of the sella turcica described by Timme but feels that the investigations of Cliff and of Gordon and Bell have shown that this slit is not characteristic of Mongolian idiocy. The treatment consisted of thyroid, thymus and pituitary extracts resulting in some improvement in special symptoms but not in the general condition.—M. B. G.

*Endocrine imbalance and its reaction to chronic arthritis*. Pringle, G. L. K., Brit. M. J. 1: 751. 1928.

The author has noticed the frequency of occurrence of rheumatoid arthritis in patients in whom an endocrine imbalance can be demonstrated. He quotes the experience of others who have likewise noticed this relationship. Especially is this true during pregnancy and the menopause. The association of arthritis with infections and septic foci is explained on the basis of an unstable thyroid-adrenal apparatus. The effect of infections on the thyroid gland is well known. In a similar manner vaccines and protein shock are at times beneficial because they stimulate the thyroid-adrenal apparatus, "sympathetic fever" being one of the normal reactions of the body against infections.

—N. A. Womack.

*Treatment of obstinate obesity*. Shepardson, H. D. and R. E. Allen, California & Western Med. 26: 33. 1927.

In the cases discussed the basal metabolism, as determined by the ordinary methods, was within normal limits, yet it was apparent that the actual metabolism was decidedly abnormal. In each instance the diet was reduced to a level considerably below the basal requirements without impairment of health, and a definite loss of weight resulted, beyond which further reduction was unobtainable by dietary restriction alone. The subsequent addition of the indicated glandular medication resulted in further loss of weight and permitted an increase in the diet to a point where moderate exercise produced no untoward effect, i. e., exercises which might have been harmful with the previous extremely low caloric intake. Thyroid extract was used as a general stimulant to metabolism rather than to supplement a thyroid deficiency. After the return to normal weight or to a point slightly below the calculated normal, there may occur a rearrangement in the weight control mechanism which will result in a maintenance of normal stature without undue limitation in diet. This form of treatment is not advocated in all cases of obesity, but in the more difficult cases when patients could be kept under close observation.—I. B.

On the internal secretions of the salivary glands (*Sulla secrezione interna delle ghiandole salivari*). Simonetta, B., Arch. Scienze Med. 49: 10. 1927.

After a careful and complete review of previous work in this field, the author describes his several experiments on rabbits deprived of parotids, submaxillary and infraorbital glands. The results, while not sufficient to deny endocrine activity of the glandular tissue as a whole, suffice to exclude with certainty that such an activity only belongs to parotids, submaxillary and infraorbital glands.—G. V.

Functional heterotransplantation of endocrine glands (*Über d. Funktion endokrinen Heterotransplantation als Kennzeichen ihrer Einheilung*). Voss, H. E., Biol. generalis, 3: 571. 1927.

Hitherto the result of heterotransplantations of various organs has been determined by microscopical methods. Voss introduces a functional test to replace or supplement the histological test in the case of heterotransplantation of certain endocrine glands, such as ovary or placenta. He transplants into rats pieces of human placenta or ovaries of mice. The hormones, either preformed in these tissues or produced by them following transplantation, call forth changes in the vaginal smear which are characteristic of proliferative processes in the vaginal epithelium like those initiated by the follicular hormone. Within the first few days following transplantation the preformed hormone enters the host organism and here exerts its typical effects (in the immature, and in some cases also in the castrated, rat). This is followed by a period of rest. Voss observes that a second period of sexual activity takes place which begins about 10 days following heterotransplantation, reaches an optimum at 18-19 days and may still be noticeable as late as 36 or even 45 days. The latest term at which some living cells were observed was 19 days after transplantation, in the case of the placenta, and 29 days in the case of the ovary. In the later periods of placental transplantation the author states that the identification of the remaining cells was not certain; he believes, however, that he had to deal with Langhans' cells. In the case of the ovary only some atretic follicles and interstitial cells were left. He concludes that these cells begin to function in the strange host organism at this relatively late date, after they have become adapted to the new environment. He believes, therefore, that the functional is superior to the histological test, as an indicator of the living condition of the transplanted tissue.—Leo Loeb.

A new method for the stimulation of endocrine glands with radium. Wolf, W., Am. J. Roentgenol. 15: 520. 1926.

Radium is distributed evenly over an area of 2 by 4 inches in a specially constructed applicator. Various types of filter may be interposed between the radium and the body to be irradiated. In every instance a hard rubber plate is interposed to absorb the secondary radiations. The length of time is 1 to 15 minutes for each gland. The distance is from 2 to 15 cm. Definite results were obtained in irradiation of the thyroid, ovaries, pituitary, testicles, and parathyroids. The results with the pineal and Islands of Langerhans were uncertain. Small doses, 0.01 to 0.1 of an erythema dose, increase the amount of glandular secretion poured into the blood stream, while large doses diminish the output.—M. B. G.

Concerning the active materials of the ovary (*Ueber die Wirkstoffe des Ovars*). Biedl, A., Arch. f. Gynäk. 132: 167. 1927.

After a short critical review of the preceding work, Biedl reports the results obtained with the oestrous hormone in his own researches. He defines the unit of this hormone as that least amount which injected into castrated mice 3 times at 12 hour intervals produces the oestrous stages of the vaginal smear. He succeeded in obtaining the hormone in a water soluble form, highly purified from follicular liquid, follicle walls and the remaining ovarian tissues by a process which depends upon the capacity of the hormone of going to the cathode upon electrodialysis. The clinical test showed the possibility of improving certain forms of amenorrhoea with small amounts injected subcutaneously and of influencing favorably the climacteric discomforts by oral

use. The dosage varied from 2-4 mouse units. In the search for the inhibiting hormone of the corpus luteum Biedl was able to find a criterion of activity but has not succeeded in obtaining the hormone itself.—Winter. Translated by J. Gagnon.

**Notes on a new hormonal test for pregnancy (A propos d'un nouveau test hormonal de la gestation).** Brouha, L., H. Hinglais and H. Simonnet, *Compt. rend. Soc. de biol.* **99**: 1384. 1929.

Subcutaneous injections of human urine were given immature female mice of 6 to 8 grams weight. After 5 days they were killed and examined. Definite histological changes in the ovaries and genital tract always indicated that the urine was from a pregnant woman. Lack of such changes was absolute evidence of non-pregnancy. Certain animals showed an equivocal reaction which left the diagnosis doubtful. Anterior lobe secretion from the hypophysis may be the hormone responsible for these reactions.—J. C. D.

**Action of liposoluble extracts of testis on the female genital tract (Action d'extraits orchitiques liposolubles sur le tractus génital femelle).** Brouha, L. and H. Simonnet, *Compt. rend. Soc. de biol.* **99**: 41. 1928.

Liposoluble extract of bull's testis produces in rats precocious puberty with the accompanying changes in the ovary and in spayed animals a return of normal oestrous.—J. C. D.

**Results of total ligation of the testicular pedicle in the domestic cock (Les effets de la ligature totale du pédicule testiculaire chez le coq domestique).** Caridroit, F., *Compt. rend. Soc. de biol.* **99**: 1311. 1929.

Such ligation produces only temporary castration. Circulation is re-established through the periphery and enough testicular tissue eventually survives to act as a testicular graft and maintain male characteristics.—J. C. D.

**Can the testis produce female plumage in spayed domestic hens? (Le testicule peut-il féminiser le plumage d'une poule ordinaire ovariectomisée?).** Caridroit, F., *Compt. rend. Soc. de biol.* **99**: 1632. 1928.

Spayed hens showed, after moulting, cock feathering and then after two years a change to hen feathering. Autopsy showed the right gonad to be a true ovo-testis. The ovarian tissue had apparently developed later than the testicular.—J. C. D.

**Effect of splenectomy and pinealectomy on the oestrous cycle in white rats (Action de la splénectomie et de l'épiphysectomie sur le cycle oestral du rat blanc).** del Castillo, E. B., *Compt. rend. Soc. de biol.* **99**: 1404. 1929.

Splenectomy did not affect the cycle and pinealectomy did not modify body growth or the age at which the vagina opened.—J. C. D.

**Reappearance and character of the oestrous cycle following ovarian grafts in spayed white rats (Réapparition et caractéristiques du cycle oestral après greffe ovarienne chez le rat blanc castré).** del Castillo, E. B., *Compt. rend. Soc. de biol.* **99**: 1501. 1928.

The initial cycles beginning a week after the graft were marked by a shortening of the dioestrous and a prolongation of the active periods. Later cycles were normal.—J. C. D.

**Insulin and folliculine (Insuline et folliculine).** Courrier, R., *Compt. rend. Soc. de biol.* **99**: 1630. 1928.

Insulin alone does not produce oestrous in spayed animals, nor does it in any way modify the action of folliculine when injected with it. Folliculine causes abortion in rabbits. Insulin does not interfere with pregnancy.—J. C. D.



The influence of vitamin A deficiency on the oestrous cycle of the rat. Coward, Katherine H., *J. Physiol.* **67**: 26. 1929.

A vitamin A-free diet was irradiated to generate vitamin D and fed to two groups of rats, (a) young whose stores of vitamin A were depleted from early life, and (b) mature rats whose stores were unknown but not large. None had had opportunity for mating. While many results on young rats confirm other investigations, variations from these results were so great that this test is considered questionable as a criterion of vitamin A deficiency. Mature rats, placed on the diet, showed normal cycles for some time, but finally vaginal smears showed only leucocytes and later only cornified cells. No ovarian abnormalities were found at autopsy.—C. I. R.

Experimental homeoplastic transplantation of testes. Demel, R., *Arch. f. klin. Chir.* **150**: 1. 1928.

The author deals with the question of persistence and growth of homeoplastic testicular transplants. In ten rats he grafted entire testes within the tunica vaginalis. The site of these transplants was prepared by removal of the normal testis. These transplants did not persist but degenerated. In each of 16 rats he prepared a site in the scrotum for reception of a testis graft. This was done by scarification of the tunica propria, thereby provoking production of granulation tissue. When entire testes were transplanted into such areas they persisted and grew. He concludes that vascularization is the chief difficulty where persistence and growth are not obtained.—R. M. Oslund.

The female sex hormone. IX. Possible significance of the rodent vaginal spread reaction in the male blood. Frank, R. T., M. A. Goldberger and L. C. McGee, *Am. J. Obst. & Gynec.* **16**: 387. 1928.

In 60 blood samples from 47 male patients, 3 gave a threshold reaction by means of vaginal smear test in the spayed mouse, and 4 gave a doubtful (weak) reaction. All attempts to obtain a positive reaction with testicle extracts have proved negative, including testicle extracts which increased the growth of combs, wattles and ear lobes of capons. In spite of the positive reactions from male bloods, we consider the rodent vaginal smear reaction specific for the female sex hormone. No explanation is as yet offered for the occasional positive reaction in the blood of males.—R. T. Frank.

The effect of x-radiation on the spermatogenesis of the guinea-pig. Gatenby, J. B., *Proc. Roy Soc.* **104**: 351. 1929.

The effect of roentgen rays on cell mitosis is due to the destruction of lipoidal substances necessary for mitosis. The centrosome does not seem to be sensitive to the rays.—E. L.

Experimental overfeminizing and its effect on the sex of the offspring (*Experimentelle Hyperfeminierung und ihr Einfluss auf das Geschlecht der Nachkommenschaft*). Gostimirovic, D., *Biol Zentralbl.* **49**: 24. 1929.

Working on white mice, with a series of 50 control and 92 treated females, this investigator found that subcutaneous injection of an ovarian hormone, (Follikulin-Menformon) was followed by an increase of approximately 20 per cent in the ratio of males to females of the offspring. It is suggested that enlargement of the uterus at oestrus resulting from administration of the hormone favored the presumably more motile male-determining sperms. The results also make it more probable that the female white mouse is homogametic while the male produces two kinds of sex-cells.—E. P. D.

Ovarian extract after artificial menopause. Haultain, W. F. T., *Edinburgh M. J.* **35**: 180. 1928.

In practice, ovarian extract by mouth reduces the unpleasant symptoms. If this is supplemented by injections of ovarian extract, the results are better.  
—J. C. D.

**The oestrous hormone in the urine of pregnant cows.** Hisaw, F. L. and R. K. Meyer, *Proc. Soc. Exper. Biol. & Med.* 26: 586. 1929.

In the urine of pregnant cows the amount of the oestrous producing hormone increases as pregnancy progresses. In general in the later days of pregnancy great amounts of the hormone may be excreted. One cow on the 280th day of pregnancy excreted more than 6,000 rat units. Within the first 24 hours after parturition, little or no hormone was eliminated.—M. O. L.

**Observations on menopause; effects of various ovarian preparations on symptoms of menopause and on basal metabolism.** King, J. T. and Ellen Patterson, *J. A. M. A.* 91: 1423. 1928. *Abst., A. M. A.*

The effects of various ovarian preparations on symptoms of the menopause and on basal metabolism were studied. The authors concluded that corpus luteum and whole ovary by mouth and follicular extract subcutaneously are probably useless in the relief of symptoms of the menopause. Bromide or phenobarbital or a combination of the two is distinctly helpful in the treatment of such symptoms, probably not specifically but as general mild sedatives. Corpus luteum may raise a low metabolic rate in a patient at the menopause, but this effect is not sufficiently striking or constant to warrant definite conclusions. Fresh whole gland and follicular extract seemed to have no significant effect on basal metabolism.

**The action of the ovarian hormone on glycemia in normal dogs (*L'action de l'hormone ovarienne sur la glycémie du chien normal*).** Rathery, F., R. Kourilsky and S. Gilbert, *Compt. rend. Soc. de biol.* 99: 529. 1928.

In bitches, folliculine increases the glycemia produced by feeding fasting animals 20 grams of glucose. In males, the blood sugar is reduced.—J. C. D.

**New experiments on experimental hermaphroditism and the antagonism of the sex glands (*Neue Untersuchungen über experimentellen Hermaphroditismus und über den Antagonismus der Geschlechtsdrüsen*).** Lipschütz, A., *Arch. f. d. ges. Physiol.* 221: 439. 1929.

Ovaries intrarenally implanted into 14 male guinea-pigs with intact testes gave in 3 cases an ovarian effect on the mammary apparatus; in 2 animals a secretion of colostrum and milk resulted.—A. T. C.

**Experimental therapeutics of oestrous failure (*Experimentelltherapeutische Studien an Weibchen mit spontaner Zyklusinsuffizienz*).** Loewe, S., H. E. Voss and E. Paas, *Endokrinol.* 1: 323. 1928. *Abst., Physiol. Absts.* 13: 664.

Transplantation of anterior pituitary into female mice in which cessation of the sexual cycle has spontaneously occurred almost invariably brings on an oestrous period. The effect is independent of the amount of gland substance transplanted. Tyramin, histamine, and a synthetic zyκλοäthanamin are unable to produce this result.

**Pseudohermaphroditism (female type predominating).** Manning, J. B., S. Robinson and N. H. Brush, *Am. J. Dis. Child.* 35: 862. 1928.

The patient was an eleven-year-old child showing external genitalia of both sexes. Pubic hair appeared at ten years of age and enlargement of the mammary glands two months previous to the time of reporting. There was a moderate hypertrichosis on the upper lip, both arms and thigh. The pubic hair was triangular in distribution with an abundance of crotch hair. The phallus was 7 to 2 cm.; the body consisting of two corpora cavernosa; there was a tiny meatal non-patent opening at the tip of the glans with, however, a hypospadias. The vaginal opening was of normal appearance. A laparotomy performed to determine the true sex revealed a rudimentary uterus with apparently normal tubes and ovaries, one ovary showing a cystic formation. No masses were felt in the region of the kidney. The sex of the child was considered as female and the phallus was removed. Microscopic examination of the latter showed erectile tissue, but nothing distinctive as to sex in the corpora cavernosa.—M. B. G.

The effect on growth and metamorphosis of feeding ovarian tissue from normal (laying) and brooding hens to frog tadpoles (*Der Einfluss der Zufuhr von Ovarium der normalen Henne und der Bruthenne auf das Wachstum und die Metamorphose der Kqualquappen dwes Frosches*). Moschini, D. G., *Endokrinologie*, 3: 29. 1929.

Eighty-six tadpoles were divided into 4 groups. Group 1 were fed beef heart and normal ovary; group 2, beef heart and ovarian substance from brooding hens; group 3, beef heart and normal hen flesh; group 4, beef heart and flesh from brooding hens. Both ovary and flesh from brooding hens produced earlier development than that from a normal or laying hen. The ovarian tissue in both cases caused earlier development than the flesh.—B. C.

The effect of the corpus luteum on the continuance of pregnancy (*Rapporti fra funzione del corpo luteo ed evoluzione della gravidanza*). Ottorino, Da Re, *Arch. di fisiol.* 26: 243. 1928.

Rabbits, in which the stages of pregnancy were known, were used to determine whether the ablation of the corpora lutea affected the continuance of pregnancy. Three animals were ovariectomized at 10 days of pregnancy and 4 animals at 20 days of pregnancy. All 7 aborted their young in from 2 to 6 days after the operation. Six control animals, 3 of which were in 10 days of pregnancy and 3 in 20 days of pregnancy, were opened laterally, followed by manipulation of the uterus and ligation of the ovarian peduncle. There was no abortion in the control group. In other experiments the destruction of the corpora lutea by cautery in 8 animals which were in 10, 11, 20, 21 and 22 days of pregnancy aborted their young in all cases. Three control animals in 10, 11 and 22 days of pregnancy received similar treatment, except portions of the stroma of the ovary were cauterized instead of the corpora lutea. Two of the controls gave birth to living young and one aborted after having contracted peritonitis from the operation. The presence of only 2 corpora lutea at the tenth day of pregnancy was sufficient to prevent abortion, while in another animal the presence of parts of corpora lutea were not sufficient to prevent abortion. The cauterization of the corpora lutea of one ovary and not the other seemed to cause abortion. The ovary, more particularly the corpus luteum, influences the normal development in pregnancy.—Earl Herrick.

On ovarian regeneration and the oestrous cycle in white rats (*A propos de la régénération ovarienne et des modifications périodiques de l'épithélium vaginal chez le rat blanc*). Pallot, G., *Compt. rend. Soc. de biol.* 99: 1333. 1929.

Total ovariectomy was performed on a dozen animals 60 to 90 days old. In 3 rats oestrus reappeared at the end of 6 months. Two of these showed regenerated ovarian tissue and the other none. Ovarian tissue may regenerate from the ovarian site and oestrus may occur without ovarian tissue being present.—J. C. D.

The functions of the corpus luteum. I. The mechanism of oestrus inhibition. II. The experimental production of placentomata in the mouse. III. The factors concerned in the development of the mammary gland. Parkes, A. S., *Proc. Roy. Soc. B.* 104: 171. 1929.

The corpus luteum was shown to be responsible for the oestrus inhibition during lactation in the mouse. Alkaline extracts of the anterior pituitary gland inhibit the oestrus cycle in the mouse due to the formation of lutean tissue. In mice sterilized by x-rays in which there were no organized follicles, the alkaline extracts of the anterior pituitary gland luteinised the remaining tissue which resulted in oestrus inhibition. Placentomata were produced in the mouse during pseudo-pregnancy, lactation, and during the inhibition of oestrus produced by anterior pituitary extract, whereas during normal dioestrus and in x-irradiated females it could not be produced. The luteal phase of pseudo-pregnancy in a non-pregnant rabbit was prolonged to the length of true pregnancy with anterior pituitary extract. This caused the final phase of mammary growth, thus showing that no foetal factor is involved in the complete development of the mammary gland.—E. L.

Notes on testicular grafts in sheep (*Expériences et observations relatives a la greffe testiculaire chez le mouton*). Porcherel, A., J. Thévenot and Perraud, *Compt. rend. Soc. de biol.* 90: 1752. 1928.

Grafting testicular tissue from one variety of sheep into another produced changes in length and weight of wool. This is a possible method of improving the yield from inferior varieties of sheep.—J. C. D.

Influence of sex hormones (male) on the basal metabolism in dogs (*Influence des hormones sexuelles [testiculaires] sur le métabolisme basal chez les animaux*). Ptaszek, L., *Compt. rend. Soc. de biol.* 90: 929. 1928.

Following castration, dogs show a fall in basal metabolism. After about three weeks there is a rise to the normal rate, followed six weeks later by a steady fall to about 65 per cent of the normal rate. This persists but can be temporarily brought back to approximately normal by subcutaneous injections of testicular extract.—J. C. D.

Some interrelations of sexuality, reproduction and internal secretion. Riddle, O., *J. A. M. A.* 92: 943. 1929. *Abst., A. M. A.*

In a study of some interrelations of sexuality, reproduction and internal secretion, Riddle asserts that it is now becoming clear that the specific conditions under which genetic factor operates and develops have an equal value with the genetic factors in the determination of anything that can be called heredity. The factors distributed by germ cells set limits to the nature and appearance of adult characteristics; so do specific conditions. The matter of the control of any characteristics can be approached from either of these two sides. Many different studies during the last decades have helped to prepare the way for this new point of view. But the complete control and reversal of sex in several forms—with its implication of the theoretical possibility of its control everywhere—together with the probable identification of the particular and specific condition (metabolic rate) which here completely overrides the influence of the genetic factor—these events have adequately demonstrated the possibility of making either of many different types of individual out of identical germinal material. Heredity is controlled whenever and wherever development is controlled. Medical science will, for example, doubtless soon be provided with a relatively pure preparation of a hormone of the anterior pituitary with which the infant can be made sexually mature, as has been done already in the rat, mouse and bird. Of course, this agent will not be used precisely thus, but the advent of this specific agent sharply illustrates one type of specific condition with which one can overcome the might of heredity; and future research is sure to provide this and other types in such variety as will bring to medicine a new kind of beneficent power.

Ovarian sarcoma in a child associated with sexual precocity. Southam, A. H., *Brit. M. J.* 1: 661. 1928.

Malignant tumor of the ovary in subjects under 10 years of age is remarkably rare. The author reports the case of a girl who, at the age of 2 years and 10 months, had some vaginal hemorrhage lasting three days. Shortly after this a swelling was noticed in the abdomen. A firm, rounded, and freely mobile mass the size of a cricket ball was felt rather to the right of the midline and below the umbilicus. A second vaginal hemorrhage occurred twenty-eight days after the previous period. There was distinct enlargement of both breasts, conforming to the adult female type, and in addition there was a marked development of the pubic hair. The tumor of the right ovary and the right Fallopian tube were removed intact. There were no evidences of metastases. The uterus appeared large for the child's age; the left tube and ovary were normal. The tumor weighed 225 grams. Microscopically, it had the structure of a small, round-celled sarcoma in which there were numerous areas of hemorrhage. There were no remnants of ovarian tissue present. Since operation, two and a half years before, the breasts decreased in size, no further menstruation occurred, and the pubic hair fell out. There has been no evidence of recurrence or metastases.—H. L.

The biological actions of the female sex hormone (Ueber die biologischen Wirkungen des weiblichen Sexualhormons). Steinach, E., M. Dohrn, W. Schoeller, W. Hohlweg and W. Faure, Arch. f. d. ges. Physiol. **219**: 306. 1928.

A concentrated placental extract has been prepared, equivalent to 50,000 mouse units per gm., and from it an aqueous solution can be made containing 500 mouse units per gm. Details of the preparation are not given in this paper. The increased tissue circulation in the mammary apparatus caused by administering this endocrine preparation is due to lowering of tonus in the peripheral vessel walls. The areola and mamilla of the albino guinea-pig are especially suited to test such preparations. The mammary apparatus of the normal virgin female is developed at about 17 weeks. It can be produced in infantile castrates after three weeks' treatment with the endocrine preparation (at the age of 7 weeks). The hyperemia is visible at the third day of treatment and can be employed as a biological test for the potency of the hormone. Histological effects on mammae and uterus are described.—A. T. C.

The changes in the ovaries and other organs of animals injected with various ovarian substances. Zerada, M., Japan M. World, **7**: 233. 1927.

Follicular fluid and autolysates of corpus luteum and interstitial gland were injected intraperitoneally into adult female rats. All of the materials injected caused a degeneration of the interstitial gland of the ovary, and interfered with the normal development of follicles. Mature follicles were caused to rupture, and immature ones to develop into cystic follicles. The ovaries of young animals were but little influenced by the autolysates and follicular fluid.  
—M. O. L.

Concerning the primateship of the ovum (Ueber das Primat der Eizelle). Westman, A., Acta obst. gynec. Scandinav. **1**: 166. 1928.

Previous theoretical considerations of other authors are discussed with reference to the possibility that ova in transit might influence the development of corpora lutea and corresponding changes in the endometrium. The author has been able to eliminate all influence exerted on the experimental animal by the ova cast off at the time of follicle rupture by doing bilateral salpingectomy on rabbits when all ova are located in the tube on their way to the uterus. In spite of this procedure the corpora lutea as well as the uterine mucous membrane have, anatomically, passed through exactly the same cyclical development as that found in so-called pseudo-pregnancy. The experiments show that the development and function of the corpus luteum are not conditioned by products of absorption from ova liberated from the follicles. Four illustrative experiments are cited. The experiments were carefully controlled. The results seem conclusive.—J. P. P.

Histology of ectopic testes. Interstitial tissue and secretory phenomena (Histologie du testicule ectopique. Tissu interstitiel. Phénomènes sécrétoires). de Winiwarter, H., Compt. rend. Soc. de biol. **99**: 645. 1928.

Two cases, of subjects 23 and 40 years old, are described. There was atrophy of the interstitial tissue in both cases.—J. C. D.

Constipation treated with pituitrin. Ambrose, C. D., Pennsylvania M. J. **32**: 428. 1929.

This is a brief discussion, with two illustrative cases, on the use of pituitrin in intestinal sluggishness. In comparison with eserine it may be said that pituitrin is more prompt and violent, while eserine presents an effect of much longer duration.—I. B.

Hypophyseal "Geographical skull" (Ueber hypophysären Landkartenschädel). Brehme, T., Ztschr. f. Kinderh. **46**: 401. 1928.

The present case is in a boy of 4½ years who, following a mild trauma, presented softening of the skull bones and symptoms of diabetes insipidus—an increased thirst, increased urine output and a urine with a low specific gravity

and a diminution in NaCl excretion. The administration of pituitrin was followed by a diminution in diuresis, but not in thirst. Novasurol produced a diminution in thirst, an increase in urine NaCl concentration and a lowering of the serum NaCl. The patient was on a salt-free diet.—M. B. G.

**On the mode of action of certain extracts of anterior lobe of hypophysis** (*Sur le mode d'action de certains extraits du lobe antérieur d'hypophyse*). Brouha, L. and H. Simonnet, *Compt. rend. Soc. de biol.* 99: 759. 1928.

Extracts, both acid and alkaline, were injected into rats. One to six doses were given. The onset of oestrous was delayed in young animals and in adults oestrous was suspended. The authors assume that this is due to an accentuation of the effect produced by the corpora lutea.—J. C. D.

**The rôle of the anterior pituitary in compensatory ovarian hypertrophy.** Engle, E. T., *Anat. Rec.* 37: 275. 1928.

Unilaterally ovariectomized and normal mice and rats were given the same number of daily homeotransplants of the fresh anterior lobe. The weights of the ovaries were compared with those in untreated unoperated and untreated ovariectomized litter-mates. The remaining ovary from unilaterally spayed animals which had the same treatment as the unoperated animals was found to weigh approximately twice as much as the combined ovarian weight in the unoperated, treated animals. Variations in ovarian weights of the treated animals occurred due to physiological limits of response of an organ to increased stimuli, as well as to constitutional factors. In the mouse and rat, at least, it is shown that the anterior lobe of the pituitary furnishes the stimulus for both the structural and the functional hypertrophy of the ovary observed in these experiments.—Author's Abst.

**The effect of daily transplants of the anterior lobe from gonadectomized rats on immature test animals.** Engle, E. T., *Am. J. Physiol.* 88: 105. 1929.

The ovarian response of immature mice and rats following the daily transplantation of the fresh anterior hypophyseal lobe taken from gonadectomized rats is significantly greater than the response to anterior lobe transplants from normal animals. There is no sex difference in the biological potency of the glands of gonadectomized donors, and no significant difference as regards the age of the donor at the time of gonadectomy. While the pituitary of the gonadectomized animal is larger than that of the normal, the ovarian response to the former is so great that storage of the gonadal-stimulating factor is thought to occur. These data offer further evidence which points to a gonadal-pituitary "releasing mechanism," the presence of the gonad being the prime factor involved in the release of this hormone from the organ of origin.

—Author's summary.

**Impairment of the birth mechanism due to hormones from the anterior hypophysis.** Evans, H. M. and Miriam E. Simpson, *Proc. Soc. Exper. Biol. & Med.* 26: 595. 1929.

A hormone of the anterior hypophysis (distinct from the growth hormone) which causes precocious maturity in young female rats, also causes growth of lutein tissue in the ovary. This substance also causes interference with the birth mechanism by prolonging pregnancy 2 to 3 days.—M. O. L.

**Stimulation of placentoma reaction in virginal endometrium by treatment with anterior hypophyseal hormone.** Evans, H. M. and Miriam E. Simpson, *Proc. Soc. Exper. Biol. & Med.* 26: 597. 1929.

The anterior hypophyseal hormone which promotes precocious development of the immature ovary has the same stimulating effect on placentoma formation as does the growth hormone. These substances also cause hyperplasia of the mammary apparatus of 24-day-old female rats, before lutein structures were present in the young ovaries.—M. O. L.

**Therapeutic experiments with pituitrin in gastric atony of nurslings and infants** (Therapeutische Versuche mit Hypophysin bei Magenatonie im Säuglings- und Kindes-alter). Koenigsberger, E. and W. Mansbacher, *Ztschr. f. Kinderh.* 44: 265. 1927.

Studies were carried out in cases of chronic gastric atony, habitual vomiting, marked loss of appetite and marked motor insufficiency of the stomach in dystrophic infants and also in cases of acute gastric atony in any type of child with an acute infection. In addition to the hypodermatic administration of pituitrin, the treatment consisted of lavage, rest period and then gradual increase in feeding. The dose of the pituitrin was 1 cc. after meals, following a three-hour rest. Pituitary extract was used because of its action on unstriated muscle. It was found to act as a gastric stimulant in small doses and as a deterrent in large doses. The authors consider it a valuable therapeutic agent in the treatment of gastric atony. If the pituitrin itself is ineffectual, it may be combined with either adrenalin or atropine sulfate, the combination of pituitrin and atropin being found more efficacious. The dosage will at times depend on individual tolerance.—M. B. G.

**Histological evidences of colloid absorption directly by the blood vessels of pars anterior of the human hypophysis.** Rasmussen, A. T., *Quart. J. Exper. Physiol.* 17: 149. 1927.

From the literature, which is reviewed, one is given the impression that the presence of colloid in the blood vessels of the hypophysis is not an uncommon occurrence. As a result of systematic examination of a hundred normal adult hypophyses (mostly males from cases of sudden accidental death) with oil immersion lens, only two showed any evidence of colloid in the blood vessels. Colloid was especially abundant in the blood spaces of the anterior lobe and in the veins of the capsule and of the infundibular stalk in a young, pregnant female. The method by which the colloid entered the blood stream is not evident. This study indicates that colloid is seen in the blood vessels of the hypophysis in only a few per cent of normal cases.—Author's summary.

**Suprapituitary tumor (?)**. Schlesinger, B., *Proc. Roy. Soc. Med. (Sec. Dis. Child.)* 21: 217. 1927.

The case described occurred in a girl of 9 years, whose congenitally large head became increasingly more out of proportion to the size of the body. The circumference of the head was 24½ inches. Hydrocephalus and closed fontanelles were present. There was a deep optic neuritis and a double extensor response. Visual fields were peripherally diminished. X-ray examination showed the sella turcica to be much enlarged, deepened and rounded, and the clinoid processes were not visible.—I. B.

**The effect of infantile and foetal anterior lobe transplants on infantile gonads** (Tierexperimentelle Untersuchungen über die Wirkung infantilen und fetalen Hypophysenvorderlappenhormons auf infantile Keimrüsen). Siegmund, H. and A. Mahnert, *München. med. Wchnschr.* 75: 1835. 1928.

The activating influence of the anterior lobe in the gonad is demonstrable by means of transplants from foetal and infantile sources. Anterior lobes from foetal and suckling calves gave positive reactions when implanted into young female mice. Transplants also gave positive results when taken from human foetuses from the fifth or sixth to the tenth lunar month, a gland from a single foetus being transplanted to the test mouse.—E. T. Engle.

**Experimental evidence regarding the rôle of the anterior pituitary in the development and regulation of the genital system.** Smith, P. E. and E. T. Engle, *Am. J. Anat.* 40: 159. 1927.

Daily transplantations of mammalian anterior pituitary tissue induce precocious sexual maturity in female rats and mice at approximately half the age that maturity normally occurs. This precocious maturity is evidenced by the changes in the genital tract characteristic of normal sexual maturity and also by mating. The ovaries weigh considerably more than those of animals ma-

turing normally, having a greatly increased number of normal follicles and corpora. Superovulation is induced, as many as 48 ova occurring in a single tube. The uterine weights equal those of normally maturing animals. Transplants from immature and senile animals are effective. Immature, but not mature, males respond to the transplants. The testes, however, exhibit a lesser response than remaining parts of the genital tract. The transplants act directly on the gonads and through them on the other genital organs. Transplantations of glands other than the anterior pituitary do not hasten sexual development nor have glandular extirpations, except of the gonads, interfered with the effectiveness of pituitary transplantations. The ovaries of adult females show a profound response to the transplants. Cystic follicles occur in adult treated rats. The findings in treated normal animals harmonize with those secured from hypophysectomy and a replacement therapy. It is concluded that a hormone of the anterior pituitary is responsible for follicular development. The bearing of this on the causation of atresia, ovulation, compensatory gonadal hypertrophy and cyclic changes of the genital tract is discussed.—P. E. Smith.

**A method for early diagnosis of bitemporal hemianopsia in tumors of the pituitary** (Eino Methode zur Frühdiagnose der bitemporalen Hemianopsie bei Hypophysentumoren). Wiesli, P., Schweiz. med. Wchnschr. 58: 479. 1928.

The author utilizes a modification by Vogt of the Bjerrum method for the delineation of visual fields. Using the Förster, Bjerrum and Vogt methods in a series of cases, he demonstrates that the latter will detect hemianopsias that are not recognized by the others. He regards the method as capable of defining pituitary or other brain tumors in an incipient stage before fluoroscopy yields definite results. Several fields are reproduced and several illustrative case protocols included.—A. W. R.

**Acromegaly; amyotrophic lateral sclerosis.** Worster-Drought, C., Proc. Roy. Soc. Med. 22: 1. 1928. (Clin. Sec.)

The patient was a male of 54 years whose chief complaints were headache, weakness, enlargement of the hands and defective vision. The onset about six years ago was associated with unsteadiness of gait, occasional headaches and visual impairment. A year later both hands became enlarged and weak, and later the head was increasing in size. During the past twelve months the headaches became very intense, with increasing drowsiness. The voice too became less clear and there was dysphagia. The pulse rate was 64, blood pressure 100/70, with subnormal temperature. X-ray examination revealed general enlargement and thickening of skull bones with the pituitary not definitely enlarged but irregular in outline. There was a calcified pineal body and a general enlargement of the small bones of the nose. Considerable bony proliferation in the joint between 11th and 12th dorsal vertebrae was observed. Mentally, the patient was lethargic and irritable and exhibited a very poor memory. There was more evidence in favor of acromegaly than of atypical Paget's disease. The other feature of interest was the association, probably accidental, of amyotrophic lateral sclerosis.—I. B.

**Two cases of suprapituitary tumor (Adamantinoma).** Wyllie, W. G., Proc. Roy. Soc. Med. 22: 163. 1928. (Sec. of Laryngology.)

The first patient was a girl of ten with a history of headaches, chiefly frontal, shaking of the hands for twelve months, and increasing obesity. There was no visual complaint or increase of thirst or of micturition. Both optic discs showed papilloedema. There was tremulousness in walking and in the use of her hands. A skiogram of the skull showed advanced erosion of the sella turcica. The second patient was a girl of 21 who had always been fat but who developed excessive obesity at the age of 15 years. She showed no sexual dystrophy. Both discs showed secondary optic atrophy with a slight degree of swelling. There was some restriction of the visual fields, most marked in the temporal veins. A skiogram of the skull showed marked erosion of the sella turcica, with calcification above.—I. B.



**Anterior lobe and ovary (Hypophysen Vorderlappen und Ovarium).** Zondek, B. and S. Ascheim, Arch. f. Gynäk. 130: 1. 1927.

The authors attempted to affect the sex organs of mice by implantation of various endocrine tissues. Only implantation of the anterior lobe of the hypophysis gave positive results. A single implant of anterior lobe, taken from the beef or the human of either sex induced sexual maturity in from eighty to one hundred hours in female mice. This hormone acts only on the ovary; the uterine response is dependent upon the ovary.—E. T. Engle.

**Ovulation in pregnancy brought about by anterior pituitary hormone (Ovulation in der Gravidität ausgelöst durch Hypophysenvorderlappenhormon).** Zondek, B. and S. Ascheim, Endokrinol. 1: 10. 1928. Abst., Physiol. Absts. 13: 664.

Under the influence of the active principle of the anterior lobe of the pituitary body the ovary of the pregnant mouse is stimulated. Follicles ripen and burst and ova reach the Fallopian tubes, and in some cases show chromatin filaments in the nucleus. Corpora lutea are formed in the ovary, and sometimes a living foetus in the uterus.

**High carbohydrate diet in under-nourished diabetics (Kohlehydrat-mastkuren bei tenerernährten Zuckerkranken).** Adlersberg, D. and O. Porges, Wien. klin. Wchnschr. 41: 1298. 1928.

While previously the authors noticed improvement of tolerance of diabetic patients by the use of heavy protein or carbohydrate diets which were poor in fat, now they find as best routine a low fat, high carbohydrate diet, and give at the same time plenty of insulin to get the patient sugar free. The basis for this procedure is the change of a fatty liver of the diabetic into a glycogen-rich liver. The diet used is as follows: 200-250 gm. meat (weighed after cooking), 3 eggs, 50 gm. fat and enough carbohydrates to make up 3000-4000 calories. Any carbohydrate can be used, even sugar. The patient is kept on this diet 2-4 and even more weeks. This is enough insulin to render the patient aglycosuric; during this course the quantity of insulin required decreases rapidly, and the patient gains markedly in weight. After this there usually follows considerable improvement of the patient's tolerance. Thus, for instance, where at first the sugar output was 35 grams and urine acetone one plus, the sugar and acetone disappeared.—H. J. J.

**Danger in the postoperative use of insulin.** Andrews, E. and K. Reuterskiöld, Surg. Gynec. Obst. 47: 665. 1928.

In postoperative acidosis and dehydrated conditions glucose and water are needed, but insulin is contra-indicated.—A. T. C.

**Case of fatty atrophy following insulin injections.** Awrounin, H., Proc. Roy. Soc. Med. 22: 156. 1928. (Clin. Sec.)

A female aged 56 years had suffered from diabetes mellitus for 15 years. Her urine had been intermittently sugar free, but she did not keep to a strict dietary. Insulin therapy was begun in March, 1927, 20 units twice daily being injected into the arms, more or less in the same area each time. A year later she noticed a dimpling of the arms in the injection area. An examination of the well covered arms showed a deep depressed area on each side at the point of injection below the insertion of the deltoid, where the subcutaneous fat seemed to have entirely disappeared; skin and underlying muscles appeared perfectly normal and were not adherent; the function of the arm was not impaired. The thighs showed an early stage of same lesion.—I. B.

**Spontaneous hypoglycemia (Hypoglycémie spontanée).** Azérad, E., Médecine, 9: 755. 1928.

Numerous cases show the existence of spontaneous hypoglycemia, but its mechanism is not understood.—Author's Abst.

Studies on glycemia and glycosuria in normal and diabetic cases (*Recherches sur la glycémie et al glycosurie chez l'homme normal et chez les diabétiques*). Bacaloglu, C. and S. Strugariu, *Compt. rend. Soc. de biol.* 99: 1175. 1929.

There were 1.075 grams of sugar per 1000 cc. of blood in normals. The output of sugar in the urine was 40 to 85 mgm. per day. There was no close agreement between blood sugar and sugar in the urine in either normals or diabetics.—J. C. D.

Treatment of diabetes with special reference to accessory forms of treatment. Bartlett, W. M., *Ann. Int. Med.* 2: 334. 1928.

This paper is a criticism of the use of myrtillin, synthalin and glukhorment. The efficacy of myrtillin is questioned because it is usually used in mild diabetes, and there may be increased tolerance to carbohydrate which is not due to the treatment. The action of myrtillin is uncertain and unreliable. Synthalin always causes a loss of weight and lowers the blood pressure. Glukhorment owes its action to the synthalin which is added during the process of manufacture.—E. L.

Unusual increase of carbohydrate tolerance in case of juvenile diabetes. Blaisdell, E. R., *J. A. M. A.* 91: 960. 1928. *Abst., A. M. A.*

A child, 11 years of age, showed symptoms of diabetes for only two weeks, went into coma and was saved by large doses of insulin. A few months later she was able to discontinue the insulin on an 1800 calory diet, containing 80 gm. of carbohydrate. After one and a half years she was still sugar-free with a normal blood sugar, without insulin. The disease was apparently of such a short duration when coma occurred that very little destruction had probably taken place in the islands of Langerhans, and a large percentage of their cells were given an opportunity to regenerate.

The use of insulin in an out-patient department. Blotner, H., *New England J. Med.* 200: 491. 1929.

This is a presentation of methods for treating diabetics without hospitalization. Forty-eight cases were treated and all except 10 showed satisfactory results.—J. C. D.

The action of insulin on the perfused mammalian liver. Bodo, R. and H. P. Marks, *J. Physiol.* 65: 48. 1928.

Improved technic is described for perfusing the liver of a dog with blood from the same dog containing additional dextrose. Insulin in varying doses was added after perfusion was well under way. Portions of liver were removed as desired for determination of glycogen content. In normal, starved and fat-fed animals, glycogen storage was observed in the absence of insulin, but the latter stopped storage or speeded decomposition of glycogen. Adrenalin caused rapid decomposition even after previous administration of insulin. The authors suggest that the isolated liver does not respond as it does when in coöperation with other organs in the whole animal.—C. I. R.

The relation of synthalin to carbohydrate metabolism. Bodo, R. and H. P. Marks, *J. Physiol.* 65: 83. 1928.

A study of synthalin administration in rabbits. While insulin does not normally reduce liver glycogen to extreme low levels, synthalin reduces to very low levels so that the liver does not respond to adrenin and shows evidence of toxic effects. A hypoglycemia is produced which is due to neoglycogenesis. In hypoglycemia after insulin there is increased muscle neoglycogenesis, while synthalin causes muscle glycogenolysis. In addition, there is increased blood lactic acid with the respiratory quotient above unity, and a fall in blood pressure, also decreased oxygen consumption.—C. I. R.

**Diabetes mellitus in the negro race: A study of one hundred consecutive cases.** Bowcock, H. M., *South. M. J.* 21: 994. 1928.

Negroes of all degrees of pigmentation are subject to diabetes. Females are more subject to it than males. It appears at an earlier age in adult negroes than in whites. Obesity precedes it frequently. It is usually mild. Lues does not seem to be a predisposing factor.—J. C. D.

**Growth studies of children with diabetes mellitus.** Boyd, J. D. and M. V. Nelson, *Am. J. Dis. Child.* 35: 753. 1928.

This report of five years' observation of diabetic children confirms the results obtained by others and indicates that if uncomplicated diabetes mellitus is adequately controlled, it does not prevent satisfactory growth. Such control implies approximation and maintenance of normal blood sugar values and an adequate diet. The growth response of these carefully regulated diabetic children is greater than that of groups of non-diabetic children. This would suggest that the present concept of the rate of normal development for a healthy child may not equal his optimum, and that this may be better approximated by careful dietary regulation throughout childhood.—M. B. G.

**The effect of insulin on acetonuria.** Burn, J. H. and A. W. Ling, *J. Physiol.* 65: 191. 1928.

Rats were fed a high fat diet and acetonuria determined on 24-hour samples. Previous observations on seasonal variations in ketonuria were confirmed, this being much greater in summer. After insulin, ketonuria was augmented. In winter there was an increased liver neoglycogenesis on a fat diet, without muscle glycogenolysis or increased total urinary nitrogen. Insulin delayed the increased liver neoglycogenesis, which corresponded to the period of augmented ketonuria.—C. I. R.

**Case of disappearance of subcutaneous fat following subcutaneous injections of insulin.** Carmichael, E. A. (for G. Graham), *Proc. Roy. Soc. Med.* 21: 322. 1928.

In a female diabetic of 49 years, the subcutaneous fat over the left shoulder disappeared as the result of insulin injections.—I. B.

**Effect of ergotamine on digestive hyperglycemia in normal and diabetic subjects** (*Influence de l'ergotamine sur l'hyperglycémie alimentaire chez les sujets normaux et chez les diabétiques*). Coelho, E. and J. Candido de Oliveira, *Compt. rend. Soc. de biol.* 99: 1527. 1928.

Ergotamine fed with a meal reduced the subsequent rise in blood sugar in both normal and diabetic cases. It is poorly tolerated.—J. C. D.

**Diabetes in twins.** Curtis, W. S., *J. A. M. A.* 92: 952. 1929. *Abst., A. M. A.*

Only seven instances of diabetes in twins are on record, the author asserts. To these he has added six, making a total of thirteen. The existence of diabetes in twins in some cases almost simultaneously points to an hereditary background and offers a good field for the investigation of diabetes as a problem in heredity. When diabetes develops in a twin, one should consider the other potentially diabetic, particularly if the two are homologous, and any undue strain on the carbohydrate metabolism should be guarded against. The recognition of eight twins (four sets) with diabetes in a series of about 6,000 diabetic patients, when compared with the estimated number of twins in such a group, suggests a larger proportion of diabetes in twins than is the case in 'single individuals.

**Effect of insulin on the external secretion of the pancreas in a case with pancreatic fistula** (*Action de l'insuline sur la sécrétion externe du pancréas dans un cas de fistule pancréatique*). Fonseca, F. and C. Trincao, *Compt. rend. Soc. de biol.* 99: 1532. 1928.

Following a meal, the amount of pancreatic juice secreted by this patient was increased after insulin. If no meal was taken, insulin did not change the output. In neither instance was the amount of trypsin or of amylase altered by insulin.—J. C. D.

**Insulin treatment in severe diabetes mellitus (Zur Insulindauerbehandlung des Diabetes mellitus gravis).** Grantenberg, R., *Deutsche med. Wchnschr.* 51: 2141. 1928.

The author discusses 3 severe cases of diabetes which have been under close observation for periods varying from 1 to 3 years, and had to be given large doses (above 50 units) of insulin per day. The author points out the difficulty in giving insulin over such long periods of time. Patients are usually not willing to take more than 3 doses per day; if insulin has to be given in large single doses the danger of hypoglycemia presents itself. He therefore advises the use of opiates. He emphasizes strongly that to properly determine the patient's condition, more than just the fasting blood sugar should be taken during the day in order to get a definite idea as to what is the state of the blood sugar level during the rest of the day.—H. J. J.

**Latent tolerance in diabetes mellitus. A study of the effect of high sugar diets with insulin on controlled diabetics.** Gibson, R. B., *J. Lab. & Clin. Med.* 14: 597. 1929.

Diabetes controlled on maintenance diets with a fatty acid, potential glucose ratio of 1.5 and the required insulin dosage have shown a remarkable improvement in tolerance following two or three days of high sugar ingestion with increased insulin. Successive periods of high sugar diet at intervals of four or five days result usually in a progressive increase in tolerance until dietary management without insulin may suffice to control the diabetes, especially in young individuals. Two mild diabetics, previously controlled, continued to improve in tolerance without interruption of the high sugar diet except for substitutions and additions until a diet of general character was attained.—Author's Abst.

**Contribution to knowledge of insulin production (Beiträge zur Kenntnis der Regulation der Insulinproduktion).** Grafe, E. and F. Meythaler, *Arch. f. Exper. Path. u. Pharm.* 136: 360. 1928.

Previous investigations have shown that dextrose is an adequate stimulus for insulin production, and that this property belongs to all common carbohydrates and appears to be independent of the optical activity. This paper reports investigations of insulin producing activity of split products and carbohydrate-like substances. Hexosanes, glucosamin, oxalic acid, glycuronic acid and oxanthain all exercise a similar influence in stimulating insulin secretion. The action seems to depend on the presence of intact aldehyde and ketone groups.—C. I. R.

**Diabetes and hyperthyroidism.** Joslin, E. P. and F. H. Lahey, *Am. J. M. Sc.* 176: 1. 1928.

The authors report a series of 500 cases of thyroid disease in which they found 38.6 per cent glycosurias in 228 cases of primary hyperthyroidism and 27.7 per cent in 83 cases of adenomatous goiter with secondary hyperthyroidism and 14.8 per cent in 189 cases of non-toxic goiter. They found glycosuria in 13.6 per cent of non-diabetic and non-thyroid surgical patients, and 16 per cent glycosurias in 100 cases of diseases of the gall bladder. A certain degree of hyperglycemia in hyperthyroidism is often found which presents a problem for the differential diagnosis of what one should call diabetes in this group of cases, and thus the authors adopted the standard of a fasting blood sugar of 150 mgm. per 100 cc. (in hyperthyroids) or 200 or more postprandial in addition to glycosuria. According to this standard in the group studied, 75 cases were classified as diabetics. In primary hyperthyroidism 82.1 per cent of 23 cases, and in secondary hyperthyroidism 5 of 8 cases showed hyperthyroidism preceding diabetes. The incidence of hyperthyroidism in diabetes was 1.52 per cent and 2.5 per cent in primary hyperthyroidism with diabetes, and 4.3 per cent in secondary hyperthyroidism with diabetes. The incidence of primary hyperthyroidism in 4917 cases of true diabetes was 0.87 per cent and of secondary hyperthyroidism 0.57 per cent. The authors conclude that surgery greatly ameliorates the condition of these patients. For the group of potential

diabetics (not classified in their paper), they advocate careful observation for a period of years. They consider the hyperthyroid patient as somewhat more prone to diabetes than the ordinary individual.—H. J. J.

**Diabetic children.** Joslin, E. P. and Priscilla White, J. A. M. A. 92: 143. 1929. Abst., A. M. A.

The authors have made a study of diabetic children and found that in the twenty-two months ending July 1, 1928, the total mortality among 303 diabetic children has been six, or 1 per cent a year. In the six-year period between August, 1922, and July, 1928, the total mortality for 337 diabetic children has been thirty-six, or 2 per cent a year. The incidence of a diabetic heredity in a diabetic child increases with the duration of his disease and the number of his relatives. An inherited predisposition existed in 17 per cent of the patients who died; it has already reached 35 per cent among the living and 44 per cent among those children whose disease is of more than ten years' duration. Perhaps all diabetes in children is hereditary. Coma is still the cause and almost the only cause of the deaths of diabetic children and represents neglect. The present status of diabetic children is good, but the patients in whom the disease is of long duration usually show glycosuria. They mature sexually. Although one-third of the patients remain underweight, this is to be attributed as a rule to lack of close supervision, a pretuberculous state, or the onset of diabetes long before the use of insulin. Cataracts are not known to exist among 298 living diabetic children. Arteriosclerosis has been demonstrated by roentgenograms in five of twenty-nine children whose disease is of five years' duration or more. Only one of these five children had been on a high carbohydrate diet. Tubercle bacilli have been found in the sputum of one patient; evident pulmonary tuberculosis was present in two cases, and the chest conditions were suggestive in sixteen cases. Of the latter, one-half were neglected because they had had diabetic coma. Overheight at the onset of the diabetes has been demonstrated as varying from 2 7/10 inches on the average for the first series of 100 cases reckoned to the nearest three months to 1 8/10 inches for the second series of fifty-two cases reckoned to the nearest year, or 2 2/10 inches to the nearest three months. Diabetic children resist all types of infections with proper adjustment of diet and insulin. Confusion between the diagnosis of coma and appendicitis is easy and serious; if there is doubt, an operation should be performed. The blood cholesterol of diabetic children is now below rather than above normal. Cholesterol is a true index of the other lipoids. Insulin reactions are distressing but almost never fatal; they interfere with the ideals of treatment but are far less frequent than one would expect because of the inherent honesty of childhood. A child with glycosuria, once carefully diagnosed as being nondiabetic, thus far appears to conform to that diagnosis in the vast majority of instances.

**Insulin and adrenin action on the blood sugar during the digestion period in experiments on angiotomised dogs (Insulin- und Adrenalinwirkung auf den Blutzucker während der Verdauungsperiode nach Versuchen an angioostomierten Hunden).** Kotschneff, Nina, Arch. f. d. ges. Physiol. 220: 628. 1928.

After a meal and injection of 1.5 cc. of a 1:1000 adrenin solution no alimentary hypoglycemia was observed. After injection of 20 to 40 units of insulin a similar result was obtained. After meat feeding under normal conditions equal sugar values were found for blood from different veins. Intravenous injection of insulin results in marked retention of glucose by the kidneys, so that the ensuing hypoglycemia is of kidney origin. After a carbohydrate meal and insulin injection there is decreased absorption from the intestines and increased retention by the kidneys. After intravenous adrenalin injection and a meat meal there is, with marked sugar mobilization from the liver, no retention by intestines or muscles, but only by the kidneys.—A. T. C.

**Studies of an insulin-resistant diabetic.** Lawrence, R. D., Quart. J. Med 12: 359. 1928.

With the possible exception of cases moribund in coma no well authenticated case is on record in which insulin in large doses has had no effect in lowering the blood sugar of the patient. Cases resistant to insulin are only

relatively and not absolutely refractory. These can usually be accounted for by the following factors which antagonize insulin action: (1) Concurrent infections and sepsis. (2) Overactivity of the thyroid, pituitary, and suprarenal glands, physiological antagonists to insulin. (3) Inefficient treatment of severe cases with high or imperfectly controlled diets and insufficient insulin. (4) Liver disease, which may upon close study be included in the third category. The case reported, as far as can be ascertained, falls into none of these categories. The case is one of a young diabetic man. Diabetes was severe from the onset in 1925, but was controlled by 40 units of insulin daily and a diet of 35 grams C, 38 grams P, and 83 grams F. The fall in blood sugar after insulin was normal at this time. A year later he required 100 units on the same diet, and six months later he was excreting 5 to 10 grams of sugar on a diet of 60 grams C, 80 grams P, and 150 grams F, with 220 units of insulin. When insulin was omitted he went into coma. None of the usual factors enumerated above were present in this case. Blood sugar studies showed features quite different from the ordinary severe diabetic. His blood sugar was lowest after a night's fast. When carbohydrate was given his blood sugar rose in spite of the large doses of insulin. This was not due to delayed insulin action or lack of absorption, because insulin, given in the fasting condition, reduced the blood sugar at the usual rate, though to a less degree than in a "normal" diabetic. The author concludes that in this case insulin cannot deal with ingested carbohydrates in the usual way, by storing it as glycogen. Although it did have its other action of checking the new formation of sugar and ketones from endogenous protein and fat, and that a factor other than insulin is lacking, perhaps some coenzyme which is necessary to the usual action in forming glycogen.—P. H. Charlton.

The insulin treatment of diabetic coma. Leake, W. H., California & Western Med. 26: 475. 1927.

Basing his views on a study of 53 cases of diabetic coma, the author arrives at the following conclusions: The symptoms of approaching diabetic coma are often misleading. Abdominal pain, nausea, vomiting, fever and leukocytosis, especially in children, may lead to the diagnosis of an acute abdominal condition. Decreased intraocular tension is a very important sign in the diagnosis of diabetic coma. It is practically always present. In addition to the liberal use of insulin, buffered with carbohydrate, the treatment of diabetic coma consists mainly in forcing fluids, warmth, elimination, and stimulation with caffeine sodium benzoate and digitalis. Not more than 25 gm. of sodium bicarbonate should be administered daily. Diabetics develop coma rapidly when deprived of insulin. Coma in these individuals is apparently more resistant to insulin therapy than in patients who have not received insulin previously. In the hands of those familiar with its action insulin often saves lives, but if used carelessly the results may prove disastrous.—I. B.

Two cases of diabetes treated by synthalin. Linder, G. C. (for F. R. Fraser), Proc. Roy. Soc. Med. 21: 324. 1928.

This report presents one successful and another unsuccessful result from the use of synthalin in the treatment of diabetes mellitus.—I. B.

Increased effect of insulin in experimental cases of impermeable kidney (Augmentation de l'action de l'insuline dans l'imperméabilité rénale expérimentale). Loeper, M., A. Lemaire and J. Tonnet, Compt. rend. Soc. de biol. 99: 19. 1928.

Action of insulin in cases of impermeable kidney in man (L'action de l'insuline dans l'imperméabilité rénale de l'homme). Loeper, M., J. Ravier and J. Tonnet, Compt. rend. Soc. de biol. 99: 20. 1928.

In rabbits, ligation of the ureters prolongs and accentuates the effects of insulin. Similar results follow in human cases where there is decreased renal permeability.—J. C. D.

**Insulin treatment of scleroderma.** Michaëlis, O., Bruxelles-Medical, 9: 560. 1929. *Abst., J. A. M. A.* 92: 1716.

Michaëlis reports a case of generalized scleroderma in a woman, aged 30. After many kinds of treatment (including antisyphilitic treatment and opotherapy with various endocrine gland extracts) had proved of no avail, the author decided to try insulin, because the patient had had attacks of local asphyxia of the fingers (Raynaud's disease). Amelioration of the condition was observed after the first few injections, and it progressed steadily notwithstanding many recurrences of the symptoms. In one year the patient received 4,970 units of various brands of insulin, combined with fifty ultra-violet irradiations which were given during the last two months of treatment. This improvement continued after the treatment had been stopped, so that the author anticipates a complete cure. The skin became soft and could be raised in folds on almost the whole body, and the patient could make many movements that had been limited or abolished before the treatment.

**The chronaxie of nerves and muscles in insulinized frogs (*La chronaxie des nerfs et des muscles de la Grenouille insulinsée*).** Olmsted, J. M. D., *Arch. Int. Physiol.* 30: 202. 1928.

Since in insulin overdosage the convulsions produced are similar to those caused by strychnine injection, this author investigated the excitability of the gastrocnemius muscles of insulinized frogs. The irritability of the heart was also measured. There was no change in the irritability of either. The excitability of the sciatic nerve does not change, but it is possible that the medulla is more irritable at the time of the convulsions. During the interval between convulsions the excitability is the same as normal.—E. L.

**The dietetic management of the diabetic in the doctor's office.** Olmsted, W. H., *Ann. Int. Med.* 2: 325. 1928.

The reasons as set forth by the author for measuring the food is that if insulin and diet are not balanced, the urine will contain sugar or the patient will experience symptoms of hypoglycemia. Secondly, definite improvement in tolerance will not follow unless the urine is kept sugar-free. In diabetic education some patients are taught to weigh or measure food by the metric system. The author has classified diabetics into three groups. The first is a group having practically no education, the second are mild diabetics with some education, and the third are intelligent diabetics, very severe cases and young patients. This last group should be taught the metric system. The method of education of the second group (mild cases) is fully considered. Food is measured by methods of the modern housewife; i. e., cupful, tablespoonful and teaspoonful. The standard half-pint measuring cup is used for measuring food. The unit of carbohydrate measurement is the level teaspoonful or 4 grams. There is included, a table which gives the amount of sugar in teaspoonfuls according to cupfuls of foods. The patient chooses foods available in such amounts as will make the number of teaspoonfuls of sugar allowed. A table of albuminous foods is also included. The unit of fat is taken as the square of butter made by cutting off one-half inch from the quarter pound package. This represents about 10 grams of fat. The table gives equivalents of fat containing foods in squares of butter.—E. L.

**The pathology of diabetes in young adults.** Page, J. H. and S. Warren, *New England J. Med.* 200: 766. 1929.

The findings in 11 patients, from 12 to 33 years of age, emphasized (1) the slight and variable changes in the pancreas, and (2) the very striking evidence of disturbance of lipid metabolism as shown by extensive atherosclerosis. —J. C. D.

**An unusual case of diabetes and gout.** Rabinowitch, I. M., *Canada M. A. J.* 19: 632. 1928.

A patient who had had typical attacks of gout five or six times a year for 10 years was admitted to a hospital with diabetes severe enough to demand insulin. Insulin treatment precipitated attacks of gout. Synthalin treatment

was attempted and initially gave rise to cramps and diarrhoea. There being no evidence of liver damage, the synthalin treatment was persisted in, and for fifteen months the urine has been kept sugar-free and the blood sugar practically normal without the use of insulin. High plasma cholesterol persists, indicating that unlike insulin, synathalin has no effect on the metabolism of cholesterol. A second case of diabetes with gout did not exhibit the anomaly, much larger doses of insulin producing no attacks of gout.—A. T. C.

**The cholesterol content of blood plasma in diabetes mellitus.** Rabinowitch, I. M., *Arch. Int. Med.* 43: 370. 1929.

Plasma cholesterol affords a reliable index to the true progress of the diabetic patient. Because of the simplicity with which the test can be carried out, estimation of the plasma cholesterol should form part of the routine management in diabetes. As with all laboratory tests, in the interpretation of results obtained consideration should be given to other conditions which might lead to high values. These include jaundice, cholecystitis, pregnancy, nephrosis, etc.—Author's summary.

**The action of insulin on regeneration.** The biological rôle of potassium and calcium ions in the process (*Die Wirkung des Insulins auf die Regeneration. Die biologische Rolle der K- und Ca-Ionen bei diesem Vorgange*). Schazillo, B. A. and M. Je. Ksendowsky, *Arch. f. d. ges. Physiol.* 220: 774. 1928.

Insulin assists bone regeneration. Injection of isotonic KCl solution subcutaneously inhibits the insulin action, but isotonic calcium chloride solution favors it.—A. T. C.

**Diabetes. Late results of insulin treatment. Treatment with synthalin.** Strouse, S. and B. Y. Glassberg, *M. Clin. North America*, 12: 79. 1928.

A brief review of the subject, with nine illustrative cases, is given. The difficulties encountered by the physician when the patient evinces little or no coöperation are stressed. Generally speaking, the authors found synthalin unsatisfactory. Aside from such symptoms as nausea, vomiting and abdominal pain, the effects in the control of carbohydrate metabolism do not compare with those following the use of insulin.—I. B.

**Pancreatic cyst with diabetes.** Timme, A. R., *California & West. Med.* 26: 349. 1927.

This is a report of a case of pancreatic cyst with papilloma of the wall of the cyst possessing some malignant characteristics. The patient was a married woman of 44 whose chief complaint was enlargement of the abdomen and pain and weakness of the legs. The latter proved to be typical neuritis associated with diabetes mellitus. There was a loss of 53 pounds in weight. The patient made an uneventful post-operative recovery and was placed under a diabetic regime of treatment.—I. B.

**Diabetes and tuberculosis.** Tompkins, R. D., *South. M. J.* 22: 143. 1929.

Thirteen cases are briefly considered. In most of these the diabetes was successfully controlled by insulin, but the tuberculosis could not be favorably influenced.—J. C. D.

**Note on the action of ergotamine on glycemia (A propos de l'action de l'ergotamine sur la glycémie).** Trincao, C., *Compt. rend. Soc. de biol.* 99: 1538. 1928.

In three diabetics, when insulin and ergotamine were given together, the reduction in the hyperglycemia following a glucose meal was the same as when insulin alone was used. In a fourth diabetic the reduction was much greater, equal to the reduction produced by ergotamine alone plus that of insulin alone. —J. C. D.



The rôle of secretin in the regulation of the alkali-reserve of the blood (*Zur Frage nach der Rolle des Sekretins bei der Regulierung der Blutalkali-reserven*). Wolnar, A. O., Arch. f. d. ges. Physiol. 221: 144. 1928.

Secretin plays a distinct rôle in the regulation of the alkali-reserve of the blood. There is a direct relationship between the variation of alkalinity of the secretin-pancreatic juice and the alkali-content of the blood. Where there is decreased alkali-reserve, at the same time there is a decreased alkalinity of the juice. Artificial increase in the blood alkalinity (by injection of sodium carbonate) increases the amount and degree of alkalinity of the juice.—A. T. C.

Response of the higher nervous centers to hypoglycemia following insulin (*Sensibilité des centres nerveux supérieurs à l'hypoglycémie provoquée par injection d'insuline*). Zunz, E. and J. LaBarre, Compt. rend. Soc. de biol. 99: 631. 1928.

Three dogs were used. The head of a dog "B" was isolated from its body, except for the vagi, and supplied with blood from dog A, in which hypoglycemia had been produced by the injection of insulin. The pancreatic vein of B was connected with the jugular of a depancreatized dog, C. All dogs were anaesthetized with chloralose. The hypoglycemia of dog A has little effect. If hyperglycemic blood is substituted, however, it acts through the blood stream on the higher centers of B. These, through the vagi, cause an increased output of insulin from the pancreas of dog B, which is indicated by a fall in the blood sugar of dog C. The higher centers, therefore, respond to changes in blood sugar and may act directly to control it.—J. C. D.

Tumors of the parathyroid glands. Guy, C. C., Surg. Gynec. Obst. 48: 557. 1929.

Adenomata of the parathyroids are comparatively rare. Apparently benign tumors of years' duration may suddenly take on malignant character. The question of true adenoma formation or of hyperplasia may be difficult to decide in enlargements of the parathyroids. Parathyroid tumors are easily confused with thyroid tumors. Their histological character shows considerable variation. —A. T. C.

Concerning the influence of the hormones of the parathyroid on the liver (*Über den Einfluss von Hormon der Epithelkörperchen auf die Leberfunktion*). Kim, M. H., Trans. Japanese Pathol. Soc. 18: 383. 1928.

In parathyroidectomized rabbits dye excretion of the liver is depressed, while the output of foreign proteins is increased. The parathyroids, therefore, have an important influence on liver excretion and on assimilation of foreign proteins.—R. G. H.

The effect of colectomy on the incidence of parathyroid tetany and the blood calcium. Oldberg, E. and E. L. Walsh, Am. J. Physiol. 85: 531. 1928.

Several series of experiments were performed. In the first series of ten dogs, the colon was removed, and about a week later the parathyroids were removed. In four dogs, tetany was not seen; in three others it was considerably delayed; and in the other three it developed in the usual time. In the second series of ten dogs, the parathyroids were removed; and on the incidence of tetany, the colon was removed. Tetany usually occurred on the second day after parathyroidectomy and again on the second day after colectomy. In the third series of two animals, the parathyroids and colon were removed at one operation. In both animals tetany occurred on the second day after operation. In a fourth series, the blood calcium was followed after colectomy in eight dogs. It was found that an increase in serum calcium occurred. The increase amounted to from 0.8 to 3.0 mgm. per 100 cc. of serum and occurred in from 4 to 7 days, and then declined to normal in about 10 or 12 days. In a fifth series, five dogs were used whose colons were removed and whose parathyroids, about 4 days later when the blood calcium was the highest, were also removed. The fall in blood calcium following the removal of the parathyroids was somewhat slower than in dogs only parathyroidectomized and somewhat higher than

usual at death. It was concluded that (1) when colectomy precedes parathyroidectomy, the onset of tetany is modified; (2) when colectomy succeeds parathyroidectomy, only a transitory depressant action on tetany is noted; (3) and that the removal of the colon of the dog causes in most cases a transitory rise of blood serum calcium of 0.8 to 3.0 mgm. per 100 cc. of serum.—Author's Abst.

**The pineal body.** Jelliffe, S. E. (Nelson's Loose Leaf Medicine, May, 1928).

This is the most complete condensed review of the literature upon the pineal that has appeared in recent years. The author neglects almost nothing, possibly with the exception of some of Pines' work upon the pineal neural connections, which, however, appeared too late in Russian literature translations or reviews to be included. The general trend of this work is to cast considerable doubt upon the endocrine function of the pineal and to emphasize its neural connections.—Author's Abst.

**Dysgenitalism of splenic origin (Le Dysgenitalisme d'Origine Splénique).** Radossaviyevitch, A. and A. Kostitch, *Rev. franç. d'endocrinol.* 7: 22. 1929.

This is a clinical and experimental study of the relation of the spleen to the female sex glands. The experimental work consisted chiefly of studying the effects of splenectomy on the production of a precocious sex cycle as determined by vaginal smears in the immature white mouse. Splenectomy produced oestrus in 17 of 22 cases. In the remaining five cases the oestrus was delayed. Clinical evidence of an inter-relation between spleen and genital glands is also given.—B. C.

**Some sidelights on the thymus vogue.** Garland, J., *New England J. Med.* 200: 59. 1929.

After an analysis of 1564 autopsy cases, 23 of which showed enlargement of the thymus, the author considers that the present vogue of x-raying for thymus and radiating all cases in which a shadow appears would seem to be unjustified.—J. C. D.

**Irradiation of the thymus gland in the treatment of psoriasis.** Jamieson, R. C., *Arch. Dermat. & Syph.* 18: 109. 1928.

The work reported was similar to that which Foerster reported in 1921, and reviews the reports of European observers who had treated psoriasis by this method. The majority of reports quoted by the author regarded this method of treatment as one which should at least be given a trial, although favorable results could be expected in only a certain variable percentage of cases. The cases reported, 50 in number, were rayed over the thymus area, using 88 kilovolts, 5 milliamperes, skin target distance of 12 inches, a 3 mm. aluminum filter, and an exposure of 3 to 5 minutes, depending on the type of patient. Many of those treated also received thymus extract orally. Ten per cent of the cases were considered to be definitely improved, thirty-four per cent showed temporary improvement, while the remainder were unimproved. The writer believes that irradiation of the thymus gland, either with or without thymus extract internally or by injection, has a certain definite, though possibly small, value in the treatment of psoriasis. It has not produced any harmful effects, but further work will be necessary to improve the technic and standardize the dose of x-ray.—Author's Abst.

**The relative sensibility of normal and involuted thymus when exposed to x-ray (Sensibilité comparée aux rayons X d'un thymus normal et d'un thymus involué).** Jolly, J. and R. Ferroux, *Compt. rend. Soc. de biol.* 99: 718. 1928.

Guinea pigs of various ages were exposed to x-ray under standard conditions. The thymus was removed six hours later and examined. Nuclear pyknosis and other evidence of active response to the x-ray was found, regardless of the degree of involution of the gland or the age of the animal.—J. C. D.

Status lymphaticus. Marine, D., Arch. Path. 5: 661. 1928. Abst., Arch. Neurol. & Psychiat. 20: 614.

This article is a comprehensive review of present knowledge of the problem of status lymphaticus. Status lymphaticus may be defined as a constitutional defect, usually congenital (although it may be acquired), dependent on an inadequacy of some function of the suprarenal glands, the sex glands and the autonomic nervous system and associated with lowered resistance to a great variety of non-specific, physical and chemical agents. Anatomically, it is characterized by delayed involution or hyperplasia of the thymus, hypertrophy and hyperplasia of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin, gonadal and cardiovascular systems and by certain peculiarities of external configuration.—Author's Abst. (abbreviated).

The so-called condition of status thymico-lymphaticus and its relation to the endocrine system (*Über den sogenannten Status thymico-lymphaticus und seine Beziehungen zum endokrinen System*). Oswald, A., Schweiz. med. Wehnschr. 58: 1173. 1928.

The criteria for the diagnosis of status thymico-lymphaticus given in this paper are: a pale skin, excessive development of subcutaneous fat pads, hypoplasia of the heart and blood vascular systems, enlargement of the thymus and lymphatic apparatus, and diminished resistance to physical, bacterial, and toxic agents, with a great tendency to sudden death. According to the author, enlargement of the thymus is not the cause of sudden death in cases of status thymico-lymphaticus, but rather reflects a disturbance of the interrelation between the thymus and the other glands of internal secretion. He also believes that the thymus may play a part in the defense mechanism against injurious humoral influences. He then cites the well-known thymus enlargement in Grave's disease, but states that there is no experimental proof of such an interrelation. The well-known enlargement of the thymus and hypertrophy of the lymphatic apparatus that is associated with absence of primary sex organs is also stated as evidence of the relation of the thymus to the other endocrines. The large thymus that is seen in acromegaly he relates to the atrophy of the primary sex glands that occurs in this disease. The most striking relation of the thymus to the other endocrines is seen in its interrelation with the sex glands.—H. L. Jaffe.

The effect of thymus on water and salt regulation (*Thymusextrakt und Wassersalzhaushalt im frühen Säuglingsalter*). Seckel, S., Ztschr. f. Kinderh. 44: 473. 1927.

The effect of thymus extract on water elimination was studied in 17 infants up to the age of six months. In the majority of experimental cases there was an incomplete total water excretion, a diminution in renal and extrarenal elimination and an evident NaCl retention. The effect of thymus extract is one of hydremia and may be considered on the basis of a tissue water retention. Secondary effects of thymus extract are a mild bradycardia, dilatation of the circulatory system and an inconstant diminution in the number of leucocytes. The blood sugar remains unchanged. Thymus extract, like the pancreas hormone, stimulates water retention and vasodilatation. Both of these hormones in this respect can be considered as vagus stimulants and as antagonists to the sympathetic action of the adrenal and thyroid hormones. The tissue water retention properties of thymus extract and of insulin permit the therapeutic combination of both of these in the management of infantile dehydration.

—M. B. G.

The condition of thyroxine in the animal organism (*Studien über das Verhalten von Thyroxin im tierischen Organismus*). Abderhalden, E. and E. Wertheimer, Arch. f. d. ges. Physiol. 221: 82. 1928.

Muscle tissue shows the greatest uptake of thyroxine. Liver tissue is scarcely affected.—A. T. C.

The fate of the thyroid hormone in the organism of hyperthyroidized mammals (Weiterer Beitrag zur Frage des Schicksals des Schilddrüsenhormons im Organismus hyperthyreoidisierter Säugetiere). Asimoff, G. and M. Lapiner, Arch. f. d. ges. Physiol. 220: 588. 1928.

Using the axolotl metamorphosis as a test, it is shown that the thyroid hormone can be detected in the blood and urine of a dog after administration of a large dose (100 gm. or more) of desiccated thyroid. It can be detected in the blood from 2 to 20 hours after administration. It leaves the organism more rapidly in mammals than in birds. The maximum excretion in urine is between 6 and 18 hours after administration.—A. T. C.

Heart-block influenced by inspiration in a case of Graves' disease. Bourne, G. (for P. Hartley), Proc. Roy. Soc. Med. 21: 322. 1928.

An unmarried white female of 34, in 1921, suffered from exophthalmic goiter. Within a year, as the result of medical treatment, she became so well as to be able to resume her occupation as typist. Following a severe attack of influenza in 1927, the syndrome recurred, excepting that the heart rate was 65 per minute. The basal metabolic rate was plus 41 per cent. Electrocardiographic and polygraphic tracing showed the presence of a 2:1 heart-block. The block was completely removed for 45 minutes by  $\frac{1}{2}$  cc. of adrenalin. It was not abolished by 1/33 gr. of atropin sulphate subcutaneously. It was increased by pilocarpine nitrate. The author suggests that the phenomenon shows the presence of inspiratory increased accelerator tone, in addition to the decreased vagal tone known to exist.—I. B.

The iodine content of the thyroid of two species of elasmobranchs and one species of teleost. Burwash, Frances M., Contrib. Can. Biol. & Fisheries, 4: 115. 1929.

The skates *Raja laevis* and *R. erinacea* contain respectively for males an average of 0.031 and 0.025 per cent iodine in desiccated thyroid tissue, and for females 0.048 and 0.049 per cent. Results for the female haddock referred to the whole weight of the fish indicate that its thyroid contains iodine of the same order as those of elasmobranchs, while two analyses for males gave values of a lower order. A hyperplastic condition of the thyroid was noted in two female *R. laevis*. One of these thyroids on analysis showed an iodine content much above normal.—A. T. C.

The vagus and the thyroid (Pneumogastrique et appareil thyroïdien). Cardot, H., J. Régnier, D. Santenoise and Vidacovitch, Compt. rend. Soc. de biol. 99: 64. 1928.

When the vagus of a dog is cut in the neck, there is increased cerebral excitability, due to the activity of the thyroid. The present experiments involved cutting the vagus in various places and showing that the effect on the thyroid was of true vagus origin and not due to the inclusion of sympathetic fibers.—J. C. D.

Roentgen treatment of thyroidal dysfunction. Carulla Riera, V., Revista Medica de Barcelona, 10: 390. 1928. Abst., J. A. M. A. 92: 1026. 1929.

Carulla Riera divides patients with hyperthyroidism into three types, the Basedowian, those who have thyro-toxic adenomas, and, finally, the patients with essential hyperthyroidism. Patients in the last group present all the symptoms suggesting that pathogenesis without showing enlargement of the thyroid. In this group and in the basedowian group, roentgen treatment yielded good results. The group with thyro-toxic adenoma is not so amenable to this treatment. Success depends largely on the correct diagnosis. There is no contraindication to the treatment and it is neither dangerous nor troublesome; all the salivary glands, however, must be carefully protected. All the author's patients received rest in the country. As these patients are inclined to be depressed, their environment must be optimistic.

**Selective growth of adult plumage in chicks treated with thyroid** (*Déterminisme thyroïdien de la poussée du plumage adulte chez les poulets*). Champy, C. and J. Morita, *Compt. rend. Soc. de biol.* 99: 1116. 1929.

Chicks treated with very small doses of thyroid showed changes of certain groups of feathers, notably those of the back of the neck, tail, and area anterior to wing. These feathers showed growth and color resembling the adult type.  
—J. C. D.

**Further observations on tryptophan and the thyroid gland.** Chang, H. C. and W. C. Ma, *Chinese J. Physiol.* 2: 329. 1928.

Experimental evidence at hand shows that the morphology of the thyroid glands of albino rats varies with body weight. The thyroids of unmated male and female albino rats of the same age may be different as their growth rates are different. The morphological evidence indicates that the heavier male has a better functioning thyroid. Litter mates of the same sex, kept under identical conditions, may show different body weights with different thyroid pictures. It is probable that the atrophic thyroid is responsible for the stunted growth, but the possibility of other endocrine glands should be ruled out. The mitochondria vary in number and shape according to the functional state of the thyroid glands. Numerous long filaments are found in the normal thyroids, while scanty rod or granulated forms are present in the atrophic glands. Tryptophan apparently has no specific morphological influence on the thyroid gland. The work thus far done on tryptophan by different investigators shows that it is not related to the thyroid hormone.—Authors' Summary.

**The complications of thyroidectomy.** Cox, H. H., *Illinois M. J.* 54: 157. 1928.

The author believes that the general mortality incident to thyroidectomy in thyrotoxicosis is much greater than is stated in the representative clinics. Thyroidectomy is fraught with dangers both during the operation and after. A thorough knowledge of the anatomy of the thyroid and its related structures is essential in the interests of safety. Hemorrhage is probably the most frequent accident encountered during the operation. Injury to the recurrent laryngeal nerve is next in order. The next most serious danger to be avoided is collapse of the trachea. Another common complication is tetany due to injury or removal of the parathyroid bodies. In the author's series of cases, parathyroid damage was demonstrated in 14 per cent; most were latent and transient.—I. B.

**Metastasis to thyroid gland from endothelial myeloma of bone; rapid regression resulting from roentgen-ray treatment.** Craver, L. F., *J. Lab. & Clin. Med.* 9: 878. 1927.

The case reported was that of a white man of thirty, who, prior to coming under the observation of the author, had an arm amputated for supposed periosteal sarcoma in one hospital, and an operation on the thyroid in another hospital for supposed carcinoma of this organ. He now presented a large mediastinal tumor, said to be an extension of the thyroid carcinoma. Examination of pathological sections from both hospitals revealed the fact that the patient was suffering from endothelial myeloma of the humerus, with metastasis to the thyroid. The remarkable radiosensitiveness of endothelial myeloma was exemplified by the rapid regression of the mediastinal mass under roentgen-ray treatment. The patient has now been apparently well for three months, although rapid recurrence is to be expected in this type of tumor.—I. B.

**Factors determining the end-results of thyroidectomy for hyperthyroidism.** Crile, G. W., *South. M. J.* 22: 137. 1929.

On a basis of extensive personal experience, Crile concludes that the symptoms of hyperthyroidism and of adrenalism are the same. Both cause increased heart action and increased pulse pressure, dilation of the vessels of the skin and sweating, dilatation of the pupils, increased metabolism, hyperglycemia, gastrointestinal disturbances, and nerve activation. The injection of adrenalin in a patient with hyperthyroidism produces an exaggeration of the symptoms of hyperthyroidism. This observation has been confirmed by experimental evi-

dence. The function of the thyroid gland is a building-up or changing mechanism; that of the adrenals is a discharge mechanism. Probably the only causes of thyroid crises are those factors which cause an increased output of adrenalin. These factors are: Pain, emotional excitation, foreign proteins, auto-intoxication, wound secretion, focal infection, infectious diseases, asphyxia, inhalation anesthesia, hemorrhage, the injection of adrenalin. Each causes an increased output of adrenalin. It follows that any plan of hospital and operative management and any post-operative regimen whereby these factors can be avoided must have a direct influence upon, must promote both the immediate and the remote results of thyroidectomy for hyperthyroidism.—R. G. H.

**The influence of thyroid preparations on the cardiac and vascular nerves.** Dreyere, H., *Quart. J. Exper. Physiol.* 19: 61. 1928.

All experimental conditions were carefully controlled and checked. Thyroid extract causes a fall in blood pressure in cats and dogs, but not in rabbits. There was no specific or constant effect on the irritability of cardiac nerves. Thyroxin had no effect on blood pressure or cardiac nerve irritability in acute experiments.—C. I. R.

**Relationship of hyperthyroidism to joint conditions.** Duncan, W. S., *J. A. M. A.* 91: 1779. 1928. Abst., *A. M. A.*

A man, aged 55, complained of nervousness, weakness, loss of weight and a rapid heart. He did not notice a goiter, but on clinical examination he manifested the classic signs of a very marked hyperthyroidism. While in the hospital a severe neuritis, so called, developed in the right shoulder and arm, which proved to be extremely incapacitating and persistent during the following 3 months of rest at home. Within this period a similar condition arose in the left upper extremity. Three weeks following admission complete thyroidectomy was performed, the wound being left open for twenty-four hours and then being closed. Section of tissues showed an adenomatous goiter. The patient was discharged on the fifth day after operation. The striking features in the patient's condition were the persistent and progressive periarticular changes involving the joints noted, which completely failed to respond to any of the recognized physical measures and forms of medication up to the time the thyroidectomy was performed. Within from forty-eight to seventy-two hours following operation the severity of the pain in the extremities had lessened almost miraculously. Three weeks following his discharge the arthritis in his right hand and shoulder was gradually giving way; no sedatives had been required since his discharge; there was yet considerable stiffness in the shoulder joint and in the right hand, but he felt confident that this would gradually disappear. Six months later there was some stiffness of his right forearm and knuckles, but the shoulders were completely normal. Similar results were manifested in the case of a woman. Whether or not the thyroid gland itself is the prime factor in the production of these cases one cannot state positively, although it seems most logical that this is another manifestation of a condition that is comparable to a toxemia which gives rise to such widespread changes throughout the body. Of the group of cases observed by Duncan, 64 per cent were females, a fact which accords with the experience of other persons particularly interested in an analysis of the so-called endocrine arthritides. In regard to the influence of the menstrual function in these cases, the majority of the patients had passed the menopause. It was noteworthy in these cases that the first signs of disease of the joints appeared at the time the hyperthyroidism was at its height and that the severity and extent of the joint involvement appeared to be in direct proportion to the severity of the hyperthyroidism. More than 80 per cent showed the earliest manifestation to be in the shoulders, and of this group over half had bilateral involvement. The author cannot agree with other observers that in this particular form of endocrine disease the joint changes are always symmetrical. Next in order of frequency of involvement were noted the knees; the metacarpophalangeal and interphalangeal joints of the hands were almost as frequently affected; next the feet and lumbar spine, and hip joints in order of frequency. In approximately half of these cases the joint involvement was multiple, with almost invariably the onset occurring in the shoulders with rapid or gradual involvement of other articulations. The degree of joint change is dependent on the severity of the hyperthyroidism and

the duration of the disability prior to the institution of radical treatment. The onset of the joint condition appeared to coincide with the height of the thyroid disease, even mild trauma in two instances acting as an inducing agent.

**Anesthesia in thyroid surgery.** Dunhill, T. P., *Proc. Roy. Soc. Med.* **21**: 345. 1928.

Thyroidectomy is an operation that should not be prolonged more than is absolutely necessary, therefore anesthesia that makes it easier for the surgeon is a direct gain to the patient. An operation on the thyroid gland will almost always cause increased secretion in the trachea which will interfere with the patient's expulsive efforts. Therefore the anesthetist should not be asked to give an anesthetic until the buccal and pharyngeal cavities are clean. Nor should an anesthetist be expected to induce anesthesia in a patient with great mental unrest or a very high pulse rate, since thyroidectomy is not an emergency operation.—I. B.

**Treatment of exophthalmic goiter.** Fenger, M., *Ugesk. f. Laeger*, **90**: 623. 1928. *Abst., J. A. M. A.* **91**: 844.

Fenger and his associates studied 543 cases of exophthalmic goiter, 362 treated medically and observed from 3 to 14 years, and 181 cases treated surgically and observed from 2 to 14 years. Their main conclusion is expressed thus: If of 200 cases of pronounced typical exophthalmic goiter, 100 are treated surgically and 100 given medical treatment, the surgeon will cure about twice as many of his hundred cases as the internist of his 100; roentgen-ray treatment does not materially affect this result.

**Antitryptic titre in pregnancy and in hyperthyroidism.** Flexner, L. B., J. Berkson, H. Winters and I. Wolman, *Proc. Soc. Exper. Biol. & Med.* **26**: 592. 1920.

With the idea that the antitryptic substances in blood serum may affect catabolism, determinations of the titre of these substances were made in cases of pregnancy and toxic hyperthyroidism, in which metabolic changes are prominent. Determinations of the titre in blood of 159 pregnant women were made. There was a progressive rise of the antitryptic titre from conception until about 170 days before parturition. Twenty-five patients with hyperthyroidism and increased basal metabolic rates showed an antitryptic titre above normal. About two thirds had a titre between plus 12 and plus 52 per cent.—M. O. L.

**The chemistry of the oestrus producing hormones.** Funk, C., *Proc. Soc. Exper. Biol. & Med.* **26**: 568. 1929.

The author believes the oestrus producing hormone of the ovary to be a phenol or alcohol forming, easily soluble salt with strong alkalis. These salts are fairly soluble in ether.—M. O. L.

**The male hormone. II.** Funk, C., B. Harrow and A. Lejwa, *Proc. Soc. Biol. & Med.* **26**: 569. 1929.

A testicular extract made by the authors showed chemical properties somewhat similar to the oestrus producing hormones of the ovary. The material was extracted from the urine of young men. The test of potency and the method of assay used were the effect on the growth of the comb in castrated cocks.

—M. O. L.

**Iodin content in the thyroid of Uruguayan cattle (*Teneur en iode des glandes thyroïdes des bovidés de l'Uruguay*).** Goslino, A. E., and M. I. Ferrero, *Compt. rend. Soc. de biol.* **90**: 1446. 1929.

The iodine content varied from .35 grams to .52 grams per 100 grams of dried gland. It was higher in cows than in steers. There were no marked seasonal variations.—J. C. D.

**The thyrotoxic symptom complex in chorea minor (Der thyreotoxische Symptomenkomplex bei Chorea minor).** Kundratitz, K., *Ztschr. f. Kinderh.* 43: 659. 1927.

The author believes that dysthyroidism is of etiological importance in chorea minor and that many of the symptoms present can be explained on a thyrotoxic basis. The appearance of the eyes is similar to that found in thyrotoxicosis. Graefs and Moebius' signs were found in only one case. The skin in chorea shows a vasolability expressed in blushing and in dermatographia. Paradoxical breathing as described by Czerny (pulling in or flattening of the thorax on inspiration) is present in both chorea minor and hyperthyroidism. The blood picture in both chorea and hyperthyroidism consists of lymphocytosis and occasionally an eosinophilia. The endocarditis in chorea may be considered as due to a thyrotoxicosis instead of to a rheumatic infection. The psychic changes, such as change of voice, irritability, restlessness and lack of concentration are similar to those found in Basedow's disease. Serejski's observation of a local regional vegetative reflex in hyperthyroidism was found in two of the children with chorea. Sweating and a flushing in thyroid region is obtained on the injection of pilocarpin. Both in cases of Basedow's disease and chorea a lowered sugar tolerance, an increased B. M. R. and increased temperature are shown. The Abderhalden test for thyroid dyscrasia was present in 81 per cent of the cases in the author's series of chorea minor. Other conditions, such as encephalitis, nephritis, impetigo, tetany and pleurisy, gave a lower percentage. The author concludes that part of the symptomatology of a fully developed case of chorea can be considered from a hyperthyroid basis. Two cases which were treated with antithyroidin gave good results.—M. B. G.

**Deductions from 6700 goiter operations.** Lahey, F. H., *New England J. Med.* 200: 909. 1929.

Based upon vessel ingrowth as a criterion, the incidence of malignancy in a group of 1484 cases of adenomatous goiter was six per cent. Adenomata of the thyroid frequently produce definite changes in the position of the trachea, as is shown by illustrations in the article. The pre-operative employment of iodine has practically eliminated preliminary pole ligation. The patient (954) operative mortality rate in all types of goitre was 0.6 per cent during the year of 1927, and 0.28 per cent in the year 1928 (1068 patients). The dangers of thyroid crises are stressed and measures to avert the occurrence of the condition suggested. There are practically no thyro-cardiacs in which the decompensation is due to a super-imposed thyroidism, that are not operable. Sub-total thyroidectomy, in thyroidism associated with pulmonary tuberculosis, or with diabetes, markedly assists in controlling the associated condition. The necessity of finding at the time of operation any parathyroid glands accidentally removed, and immediately grafting them into a sterno-mastoid muscle, is stressed and experimental indication of its efficacy submitted.—J. C. D.

**Clinical investigations into the basal metabolism in diseases of the thyroid gland.** Moller, E., *Supplementerne XXI to Acta med. Scandinav.* pp. 219. 1927.

In 70 cases of typical Graves' disease and 19 cases of the same disease in more or less atypical forms an exhaustive clinical analysis, including numerous basal metabolism determinations with Krogh's method, has been made. It was found that 7 out of 70 patients with typical Graves' disease had a basal metabolic rate within the normal limits. The author concludes that the demonstration of an increase in the basal metabolism is not essential for the diagnosis of Graves' disease. Treatment with rest and overfeeding in most cases caused the basal metabolic rate to decrease 10-20 per cent in 2 to 4 weeks. The effect of x-ray treatment was investigated in 33 cases. Good therapeutic effect was probably present in at least half of these. It was found that, as a rule, the subjective symptoms decreased earlier and more rapidly than the basal metabolic rate. Twenty-three patients with hypothyroidism (18 of which had myxedema) were examined in a corresponding manner. All of these had a decreased basal metabolism. The effect of thyroid treatment was investigated in 19 cases. Whole gland preparations, biologically standardized by the method of Jensen, were used. The increase in basal metabolic rate per unit of dose and per kgm. body weight was calculated. The use did not begin until after 2-3 days and did not reach its maximum for 2-8 weeks.—Author's Abst.



The intracutaneous salt-solution test in thyrotoxicosis. Mora, J. M., *Am. J. M. Sc.* 177: 222. 1928.

The intracutaneous salt solution test was studied in 42 cases of thyrotoxicosis, before and after operation. There was a definite decrease in the disappearance time of the wheal preoperatively. After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also became normal. In a general way, the greater the toxemia, the less time was required for the wheal to disappear. The disappearance time of the intradermally injected saline solution paralleled the basal metabolic rate as an index of the severity of the thyrotoxicosis. The literature pertaining to this test is reviewed.—Author's Summary.

The use of iodine in the treatment of goiter. Mosser, W. B., *Pennsylvania M. J.* 32: 416. 1929.

The author states that the indications for the use of iodine are: As a prophylaxis for endemic goiter; as an prophylaxis for fetal goiter; as a form of treatment of adolescent goiter; when guardedly used as a form of treatment for colloid goiter, and as a preparatory measure in the surgical treatment of toxic goiter. The drug is contraindicated: in all patients with non-toxic adenomatous goiters; in any patient in whom the goiter has persisted beyond the age of thirty, and as a form of medical treatment of toxic goiter.—I. B.

Inanition and glycogen in thyroidectomized dogs (*Inanition et glycogène chez les Chiens thyroïdectomisés*). Nitzescu, I. I. and Marie Benetato, *Compt. rend. Soc. de biol.* 99: 896. 1928.

Thyroidectomized and control dogs were starved and deprived of water. The controls could live only 20 days, while the operated animals were killed after a month. The amount of glycogen in the liver and in the muscles was greater in the thyroidectomized animals.—J. C. D.

Effect of chlorophyll and thyroxin on the sensitiveness of the organism to reduced oxygen tension (*Action de la chlorophylle et de la thyroxine sur la sensibilité de l'organisme à l'égard d'une raréfaction de l'oxygène*). Rydin, deH., *Compt. rend. Soc. de biol.* 99: 1685. 1928.

Rats injected with thyroxin are less resistant when placed under a bell jar from which the air is withdrawn than are controls or chlorophyll injected animals.—J. C. D.

Effect of chlorophyll and thyroxin on body weight (*Action de la chlorophylle et de la thyroxine sur le poids du corps*). Rydin, deH., *Compt. rend. Soc. de biol.* 99: 1687. 1928.

Thyroxin produces a cessation of growth and actual loss in body weight when injected into rats.—J. C. D.

The experimental production of hoariness and alopecia areata in the rabbit by intensive and prolonged hyperthyroidization (*La réalisation et expérimentale de la canitie et de l'alopecie en plaques par l'hyperthyroïdisation intensive et prolongée chez le lapin*). Sainton, P. and P. Veran, *Presse méd.* 36: 905. 1928.

By prolonged treatment with thyroid the hair coat of rabbits was changed from intense black to reddish black. Blanched areas next appeared, then temporary alopecia and finally the return of mixed black and white hairs.

—H. B. Torrey.

The response of chronic nephrosis to parathyroid and thyroid medication. Lewis, D. S. and W. de M. Scriver, *Ann. Clin. Med.* 2: 66. 1928.

Eppinger and Epstein both believe that this condition is due to an endocrine insufficiency, and the latter puts forward a new name, "diabetes albu-

minurica." The symptoms of endocrine origin are a lowered basal metabolism and a marked increase in cholesterol content of the blood. Response to thyroid and parathyroid therapy gives strong evidence of endocrine causation. In 5 of 7 cases reported there was a thyroid insufficiency, with a marked tolerance for thyroid extract. One case responded to parathyroid extract (Collip) by injection after thyroid extract had been tried without success. The mode of action of the parathyroid is uncertain.—M. B. G.

**Endemic goiter in California.** Searls, H. H., and P. Sharp, California & West. Med. 30: 231. 1929.

At the University of California Hospital there have been 2289 patients treated for goiter up to January 1st, 1928, and of these 1351 were of the endemic types. No case was accepted for this study where there was any doubt as to the residence at the time of development of the goiter. Maps were drawn showing a goiter belt which runs northward from Monterey County along the coast to Del Norte, then across the northern end of the state, and thence southward, with the highest incidence of all along the western slope of the Sierra Nevada. The view that endemic goiter is a direct result of iodine deficiency is given considerable support by these maps. It was found that the endemic foci lie in the mountainous regions of the northern part of the state. Here the precipitation is very heavy, and for the most part the drinking water travels but a short distance to consumption. Also some of these regions lay under the great ice sheet during the glacial period and have had the iodine washed out of their soil by the large amount of water liberated by the melting ice at the end of that time. The high incidence in the Santa Clara valley may not be accounted for by these causes. The water supply here has only recently been chiefly from wells. Wells in various parts of the world have been notorious in the development of goiter. The possibility that McCarrison's theory (on an infectious basis) explains the focus in the Santa Clara Valley, as it would seem to have in India, must be considered.—I. B.

**The tachycardias.** Shookhoff, C., M. Clin. North America, 2: 941. 1928.

This is an excellent resumé of the various forms of heart hurry, with mention of tachycardia in relation to endocrine disturbances. Tachycardias in endocrine secretory disturbances are common. In thyrotoxicosis, it is presumed that the increased or altered thyroid secretion caused an increased sensitization of the sympathetic system to the adrenalin already present in the blood. In the later stages of thyrotoxicosis, the tachycardia may be due to myocardial degeneration. Cannon and Smith believe that the thyroid secretion has a direct effect upon the heart muscle itself. The tachycardias of the menopause and those following castration are also of this type.—I. B.

**Radiation therapy in hyperthyroidism.** Soiland, A., W. E. Costolow and O. N. Meland, California & Western Med. 27: 789. 1927.

A careful review of the literature on the surgical management of hyperthyroidism reveals the fact that this form of treatment is by no means without danger, and by no means infallibly curative. Recurrence of symptoms after operation, total lack of benefit post-operatively, and other negative results are encountered. Moreover, the operative mortality rate in clinics is probably 12 to 15 per cent. Treatment of hyperthyroidism by radiation compares favorably with results obtained by surgery. Selection of patients is a prerequisite. Radiation is especially advocated in cases of so-called exophthalmic goiter, and in pure hyperthyroidism. Radiation is not associated with a mortality rate, and is better controlled than is surgery. In post-operative hyperthyroidism, again, radiation is also indicated. The frequency of the persistence of toxicity is due to thymic involvement, which is easily controlled by x-ray. There are no logical contraindications to this form of treatment, if administered by one trained in the work. Myxedema is guarded against by basal metabolic observation during treatment.—I. B.

# ENDOCRINOLOGY

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### THE EFFECT OF THE GROWTH PRINCIPLE OF THE HYPOPHYSIS ON THE FEMALE GENITAL TRACT

*With the Report of the Hypertrophic Changes in a Case of Acromegaly*

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The relation of the hypophysis to the reproductive apparatus has attracted the attention of gynecologists and clinicians since acromegaly, gigantism and the reverse states of glandular insufficiency have come to be recognized as primarily pituitary disorders. Many early experimental investigations of this problem were undertaken with the aim of clarifying the nature of the relationship. About all that came of the experiments from the point of view of genital relationships prior to the work of Smith (1, 2), Evans (3), Zondek and Aschheim (4, 5), and others, was that when the anterior lobe was largely or totally removed, either sexual infantilism or genital hypoplasia resulted, depending on the age of the experimental animal. This corresponded well with the findings in clinical hypopituitarism.

It was of course an attractive and simple deduction from these facts that if anterior lobe deficiency resulted either in failure of the genitals normally to develop or in secondary hypoplasia, excess activity would result in sexual precocity (*Frühreife*) or in overdevelopment of the genital system.

Though Goetsch (6), in 1916, believed that he had produced both overgrowth and accelerated sexual development in rats, by means of feeding experiments, his results have not been corroborated by others, and more recent work has demonstrated, at least in the case of mammals, the lack of effect of the anterior lobe hormones when administered by mouth.

With the introduction by Evans and his co-workers of the intraperitoneal administration of anterior lobe extract, an attack on the many problems relating to hypophysial overactivity was first made possible, and remarkable changes in the ovaries of the giant rats, produced by extracts containing the growth hormone, were promptly recognized. These organs were grossly enlarged and microscopically there was extensive luteinization of the walls of the Graafian follicles without previous rupture and expulsion of the ova. Indeed, the animals experienced oestrus only occasionally

or not at all during the period of injection. The uteri of these animals were not remarkable.

Using extracts of a similar nature, Putnam, Benedict and Teel (7) were able to confirm the findings in rats, but when dogs were used as the experimental subjects quite different results were obtained. In these animals, overgrowth was also produced, but the ovaries, while several times the normal size, contained no lutein tissue whatsoever. The increased size was largely due to increase in stroma with some enlarged and numerous degenerating follicles. The uterus and vagina, however, had become tremendous in contrast to the slight change produced in rats. (Fig. 1).

With the evidence produced by Smith, by Zondek and Aschheim, and by Evans and Simpson (8), which clearly demonstrated the existence of a separate gonad-stimulating substance in the anterior lobe, the interpretation of the effects from growth-promoting extracts became more difficult.

Evans and his collaborators have shown that the alkaline extracts which were used for promoting growth contain largely growth principle, but also may contain varying small amounts of the more recently demonstrated "hypophyseal sex hormone." That the great enlargement, predominantly of the uterus and vagina, in dogs treated with neutralized alkaline extracts of the anterior lobe, may be due either to the growth-promoting principle which these extracts contain or to contamination with a small amount of the so-called "sex hormone" of the hypophysis, must be recognized as alternative possibilities. While the striking effect of the gonad-stimulating principle is not to be denied, it would appear that the growth principle by itself may cause great enlargement of the genital system.

Though the laboratory will always remain our chief source of precise data regarding such complicated subjects, suggestive or corroborative information may often be secured from the clinic. It has already been shown by papers from this clinic [Bailey and Davidoff (9), Bailey and Cushing (10)] that the adenomas associated with clinical hyperpituitarism (acromegaly) are composed of acidophilic cells; that the more common adenomas causing the reverse state of acquired hypopituitarism are composed of cells of the chromophobe type; that true basophilic adenomas are unknown. Whereas the growth-promoting substance is supposed to be confined to the acidophilic cells, the experiments of Smith and of Engle (11) tend definitely to localize the gonad-stimulating substance in the basophilic cells, and it is natural to assume, therefore, that a female patient with an acidophilic adenoma and marked acromegaly in the absence of amenorrhoea would be receiving an excess only of the growth-promoting principle of the gland, the sex hormone remaining unaffected.

Complete postmortem examinations of patients with acromegaly are not common, and in the cases reported scant attention has been given to the condition of the pelvic organs. This fact was emphasized by Cushing and Davidoff (12), who found in the literature only four cases in which

the female genital system was at all adequately described, and in these it appeared that there was nothing sufficiently striking to attract notice. The hyperplasia of the genital tract appears to have been wholly overlooked,



Fig. 1.—The uterus and vagina of an acromegalic dog (left) which had been treated for 14 months with extracts containing the growth-promoting principle of the anterior hypophysis. The uterus and vagina of the littermate control are shown on the right for comparison. (Putnam, Benedict and Teel.)

and the notes on the ovaries in general called attention merely to slight enlargement, increased stroma, frequent small cysts and occasional corpora atretica.

They were able to add a description of the ovaries in two more cases. The first was a woman of 26 who had been married three years and had subsequently become amenorrhoeic. The report on the pelvic organs follows:

"The right ovary measures about 4 cm. in length and about 2 cm. in width. On section there are numerous small cystic areas. The left ovary measures about 6 cm. in diameter. On section the greater part of this is found to be made up of smooth-walled cysts containing perfectly clear colorless fluid. The ovarian tissue has been compressed and spread out and measures only 4 mm. in thickness. The uterus is 6 cm. in length and about 3 cm. in width. It is rather dark red in color. The mucous membrane is pale and of a glossy smoothness. The cervix is corrugated."

Microscopic examination revealed four large Graafian follicles, one of which might have been regarded as cystic. These follicles contained apparently normal ova. No corpora atretica and no traces of lutein tissue were seen; and only a single primordial ovum was found.

Cushing and Davidoff's second case concerned a woman who died at the age of 52 with acromegaly of long standing. The catamenia had continued for many years after the acromegaly had become apparent, the menopause having occurred at 40, twelve years prior to her death. The



Fig. 2.—Skiagram of the skull from the case presented, showing the typically ballooned sella.

ovaries were reported as small and fibrous, and no microscopic report was made. One could have hoped for but little information from the specimen, since it was obtained twelve years after the menopause.

Further light on this subject has been shed by the following case:

*Surgical No. 33265. Advanced acromegaly of seven years known duration in a single middle-aged woman without interruption of catamenia. Moderate enlargement of sella but no neighborhood symptoms. Menorrhagia, and hysterectomy for supposed fibroid. Findings: marked diffuse hypertrophy of uterus and entire genital tract.*

*Feb. 11, 1929.* First admission of Miss A. B. C., aged 49, referred by Dr. H. C. Gordonier of Troy, New York, for advice and treatment of her acromegaly.

*History.* The family history was irrelevant apart from the statement of the patient that she believed that her younger brother was developing changes in his features similar to her own. The general health of the patient had been excellent until 1922 when, at the age of 42, symptoms referable to her acromegaly first appeared. The initial symptoms were excessive fatigability and drowsiness. Two years later, in 1924, the sleepiness had become so marked as to interfere with her work. For this reason she first consulted Dr. Gordonier, who recognized the presence of early acromegaly, the manifestations of which had subsequently progressed until, according to the patient's statement, she had become unrecognizable by some of her former acquaintances.

The appetite had been voracious and she had gained about 40 pounds during the course of her malady. Except for slight diminution of visual acuity in the past three years, there had been no subjective neighborhood symptoms. Her catamenia, which had always been regular and normal, continued, without interruption, in spite of the advancing malady. For a year previous to admission, however, the flow had been somewhat scant and of offensive odor. There had been no discharge between periods.

*Examination.* This showed a well nourished woman of middle age with typical features of well advanced acromegaly, in the absence of neighborhood symptoms. The optic discs were normal and there were no constrictions of the temporal fields of vision. The x-ray films revealed a definite expansion of the sella outlines (Fig. 2) and well marked acromegalic changes in the skeleton elsewhere. The average of several determinations of the basal metabolic rate was +23 per cent and the specific dynamic action to protein, as shown by the response to a test meal of ground beef, gave a rise from the fasting rate of 23 to 41 per cent in one hour. There was no vaginal examination nor any special note made of the patient's pelvic organs.

The diagnosis of pituitary adenoma with acromegaly was unmistakable, and because of the absence of any chiasmal involvement x-ray treatment was advised. Four x-ray treatments were given,\* directed through the right and left temporal regions alternately, on Feb. 20, 21, 26, and 27th, and when the patient was discharged a few days later, definite improvement was already apparent. The drowsiness had practically disappeared, the energy and alertness had greatly increased and there was already appreciable diminution in the boggy tissues so that her gloves and shoes had become noticeably loose. The patient was discharged too soon for the change to be reflected in loss of weight as it did during the second stay in the hospital mentioned below. At the time of her discharge on March 1, 1929, the basal metabolic rate had dropped to +10 per cent.

*Subsequent note.* The patient wrote April 2, 1929, to say, that her friends remarked on the change in her appearance and that she was subjectively much improved. She wrote a month later stating that her last period was ten days late, and that when it did come there was severe menorrhagia for two weeks. A local doctor found on examination "a fibroid of the uterus as large as a grapefruit," and advised radium or return to the hospital for treatment. A subsequent period which began June 5th was of normal character and duration.

*Readmission.* *June 11, 1929.* The patient was admitted to the surgical service with the history of menorrhagia and with the diagnosis of a uterine fibroid.

*Pelvic examination.* The external genitalia were larger, more vascular and thickened than normal. The labia were particularly redundant and there seemed to be a great deal of vascular stasis. The vagina was large and the vaults were particularly deep. The cervix was large and bluish and the easily palpable uterus was symmetrical, firm in consistency, and about the size of a small grapefruit. There were no masses in the adnexal regions. *Diagnosis:* uterine fibroid.

On June 21st and 22nd while awaiting her pelvic operation two more radiation treatments were directed to the hypophysis. The patient began to lose weight immediately and the large lips and nose as well as the hands and feet visibly diminished in size from day to day. She remarked one day that she was able to see the tendons and bones of her hands for the first time in years.

*Operation.* *June 24, 1929.* (Dr. Francis C. Newton) *Hysterectomy and bilateral salpingo-oophrectomy.*

\*50% of an erythema dose. 155 Kv. 40 cm. target skin distance.  $\frac{1}{2}$  mm. copper plus 1 mm. aluminum, filter. Portals—10 x 10 cm.



Fig. 3.—The uterus with adnexa of the case presented showing the marked diffuse hypertrophy of the uterine musculature.



Under ether anaesthesia a midline incision was made and on lifting the bowel and omentum from the pelvis a markedly hypertrophied and congested genital tract was exposed. The uterine and ovarian vessels were dilated and tortuous. The uterus was symmetrically enlarged, congested and freely movable. Posteriorly, the pouch of Douglass was remarkably deep and the posterior vaginal wall with its covering peritoneum was thrown into great folds. The broad ligaments were congested, thick and of meaty consistency. Below the outer ends of both tubes there were a few small parovarian cysts. The ovaries were of good size although perhaps no larger than are often seen in non-acromegalic women. The left ovary was bound to the posterior aspect of the uterus and broad ligament by a number of old adhesions. There was a small hemorrhagic cyst in the right ovary.

The uterus, both tubes and ovaries were removed on the assumption that the uterine enlargement was due to an intramural fibroid.

*Subsequent notes.* The patient made an excellent surgical recovery. Doubtless as a result of the preoperative x-ray treatments the subsidence in the size of the extremities progressed with a total loss of weight amounting in all to 7.4 kgm. by the time of her discharge, July 13, 1929.

*Pathological description.* The gross specimen weighs 510 grams. It consists of a symmetrically enlarged uterus, with both tubes and ovaries. Below the outer end of either tube are a number of small parovarian cysts (Fig. 3).

The uterus measures 12x11x7 cm. and is of a uniform, somewhat soft consistency. On section the cut surface bulges slightly; the wall measures 4½ cm. in thickness, and appears to be composed of rather coarse bundles of interlacing fibres. No gross tumor mass is found. The endometrium is somewhat thickened and shows numerous fairly firm elastic polyps which appear to be completely covered with epithelium.

The tubes are not remarkable although they are of large size and hyperaemic.

The right ovary measures 4½x2½x2½ cm. and contains a cyst 2½ cm. in diameter which is filled with blood-stained fluid.

The left ovary measures 3½x2½x1½ cm. The surface is markedly scarred although the fluctuant consistency suggests that internally it is cystic.

*Microscopic examination.* The uterus shows a very thick wall composed of normally arranged smooth muscle bundles with no suggestion of leiomyomatous formation or fibrosis. The musculature, while hypertrophied, appears entirely normal. The endometrium shows hyperplasia with abundant loose textured stroma and a moderate increase in the number of endometrial glands. Section of a polyp shows it to be of the usual mucous variety.

The tubes show little change apart from numerous dilated thin-walled blood-vessels.

The right ovary shows on microscopic examination a corpus luteum with hemorrhage into the central portion, the hemorrhage being surrounded by several layers of atypical lutein cells. The left ovary shows numerous corpora albicantia, several follicular cysts and a rather dense ovarian stroma.

*Pathological diagnosis.* Hypertrophy of the uterus, hyperplasia of the endometrium with mucos polyps, and simple cysts of the ovaries.

#### COMMENT

The case presented is of particular interest for two reasons. First, although the patient had had advancing acromegaly for seven years, with an enlarged sella, and was 49 years of age, the catamenia had been remarkably regular and of normal character. Second, the changes in the genital tract resembled in many respects those found in dogs with experimentally produced acromegaly—namely, marked hyperplasia of the whole genital tract without striking histological changes in the ovary.

We may assume in this case that the acromegaly was an expression of an eosinophilic adenoma which had in no way affected the function of the

basophilic cells; that the genital hyperplasia therefore may be looked upon as a direct effect of the activity of the eosinophilic adenoma.

The marked similarity between the genital system in this case, in which there was presumably an increased secretion of the growth-promoting substance alone, and the genital hyperplasia induced experimentally in dogs by means of alkaline extracts of the anterior lobe which certainly contain predominantly growth-promoting substance, would indicate that the growth-promoting principle may produce marked hyperplasia of the genital tract in the female.

The hyperplasia may be regarded merely as an hitherto unrecorded expression of the visceral splanchnomegaly that characterizes the disease.

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# PITUITARY TUMOR ASSOCIATED WITH GYNECOMASTIA

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The following case of pituitary tumor illustrates what is already so well known, namely, that the pituitary gland influences the sex development of the individual. This case illustrates how certain types of pituitary tumor may produce an inversion of the sex characteristics.

The patient, a man of 52 years of age, referred by Dr. L. Adler, was admitted to Harper Hospital on May 21st, 1929, with a *history* that for about a year he had had vertigo and headache in the frontal region and impotency for the last two years. He had noticed that during the past two years his breasts were increasing in size and were taking on so-called female characteristics. Vertigo had increased over the period of the last year and in the last month previous to admission it had become very much worse. The headaches likewise increased.



Fig 1 Photograph of patient described in text

There was no complaint about vision. Four weeks prior to admission he began to notice a gradual loss of the use of the right arm and drooping of the right corner of the mouth. His speech became so much affected that he was able to speak only in monosyllables. The impotency had developed gradually, beginning two years ago.

*Physical examination* revealed a heavy set man weighing about 170 pounds and 5½ feet in height. The reaction of the pupils was normal and there was no nystagmus. The right angle of the mouth drooped to a marked degree. There was marked pharyngitis present and the tonsils were very large. An adenomatous

goiter involving both lobes of the thyroid was present. The breasts were definitely of female type and were very pendulous. The pigment of the areola and nipple showed definite female characteristics. He had a female distribution of the pubic hair. The axillary hair was rather sparse. The development of the hair on the upper lip was good. The patellar reflexes were diminished on the right, normal on the left. No Babinsky sign could be elicited on either side. There was spasticity and increased reflexes of the right arm. The testicles were very small, about one-half normal size. There had been involuntary urination for about one month. The temperature was normal, pulse 84, blood pressure 150/70.

*Laboratory Findings:* Microscopic examination of the urine revealed many pus cells. The blood nitrogen was 54.5 mgm. per 100 cc. blood; the fasting blood sugar was 0.111 per cent. Blood examinations showed: W. B. C., 10,000; P. M. N., 69 per cent; S. M., 20 per cent; L. M., 11 per cent; R. B. C., 4,860,000; Hb., 80 per cent.

Examination of the spinal fluid gave normal findings throughout.

The blood Wassermann reaction was negative on two occasions.

The basal metabolic rate was minus 15 per cent. A glucose tolerance test was made. The fasting specimen showed 0.083 per cent; at  $\frac{1}{4}$  hour, 0.117 per cent;  $1\frac{1}{2}$  hour, 0.143 per cent;  $2\frac{1}{2}$  hours, 0.111 per cent.

*X-ray examination* of the skull revealed some thickening of the inner table in the right frontal region. "The sella turcica is enlarged and there is erosion of

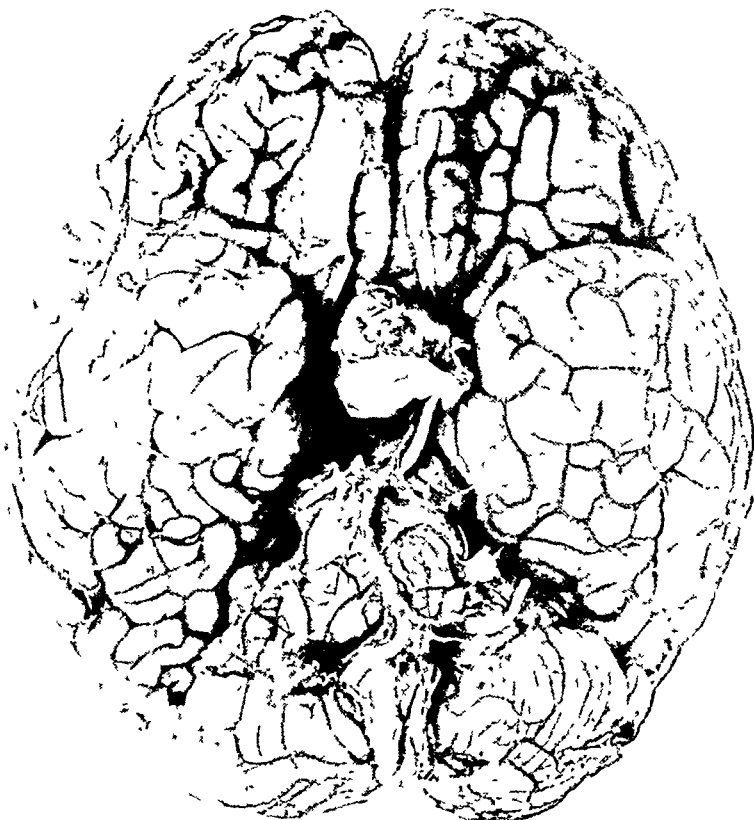


Fig. 2. Under surface of the brain, showing pituitary tumor encroaching upon the left cerebrum.

the floor and dorsum sella. Conclusions: The erosion of the floor posteriorly and the changes in the sella would indicate a pituitary tumor."

*Ophthalmoscopic examination* revealed atrophy of both optic discs. The nerves were whitish blue and the outlines of the discs showed some edema with veins fuller than normal and slightly tortuous, indicating pressure. The tension was normal. The examiner was "unable to get vision or perimetric fields on account of the patient's mental condition and lack of coöperation."

On May 27th, ascending lipiodol,  $7\frac{1}{2}$  cc. was injected into the spinal canal. X-ray examination of the skull following this injection showed the lipiodol in the fourth ventricle in the cisterna magnum. "There were a few droplets which apparently had passed into the lateral ventricles. We do not believe, however, that the lack of filling with lipiodol could be interpreted as indicating an obstructive lesion between the third and lateral ventricles. The distortion of the sella turcica previously described is again evident."

Two days after the injection of the lipiodol, during the afternoon, the patient's temperature rose to  $101.6^{\circ}$ , pulse to 130, and respirations to 22. On May 30th, 1929, the axillary temperature was  $101^{\circ}$ , the pulse 148, and respirations increased to 48, and the patient went into coma. The respirations became very



Fig 3. Photomicrograph of a section of the tumor.

rapid and shallow and there was free diaphoresis present. On May 31st, the patient was still comatose with pulse 160 to 170 and respirations 48. He expired on May 31st, 1929, at 11:45 p. m.

The *post mortem* examination was limited to the head. This is to be regretted in view of the fact that it would have been interesting to study suprarenals and testicles.

Report of the autopsy is as follows: "The subject is an extremely obese, middle-aged male. The distribution of fat is strikingly that of a female. The breasts are very large and pendulous. The pubic hair line is straight across, just above the pubis. The axillary hair is scanty. The testicles are small.

"On opening the dura, globules of oleaginous material were seen to be present in the spinal fluid. (This was lipiodol previously injected intrathecally.) The pia arachnoid is thick and edematous and the blood vessels are engorged. On lifting the frontal lobes a large tumor is seen in the sella turcica which has been greatly enlarged. The posterior clinoid process of the sella is not present on the left side, where the tumor is mostly asymmetrical. The tumor has stretched the optic chiasm so that it is like a small band  $\frac{3}{4}$  inch long extending between the optic nerves. The tumor is about  $1\frac{1}{4}$  inches long and pear shaped, with the small point attached to the region of the infundibulum. The tumor is solid and has the consistency of a testicle."

The pathological diagnosis was: "*Pituitary adenoma.*"

*Microscopical examination:* "The tumor consists of a rather histoid mass of cells of uniform character arranged within a delicate connective tissue stroma carrying the large thin walled veins. There is a definite tendency to alveolar



Fig. 4. Photograph showing the atypical cells in the capsule surrounding the pars intermedia.

and nest-like arrangement, although in places this is lost and the structure becomes uniform. The atypical cells are invading the capsule of the tumor and surround the pars intermedia, which appears normal as to follicle structure and colloid material.

The individual cells in the hematoxylin eosin stain closely resembles a plasma cell in staining qualities, size and nuclear structure. The nucleus, however, is not uniformly eccentric, but is more centrally placed.

With the ethyl-violet, orange G. stain the cells are found to be uniformly of the chromophobe type.

*Diagnosis:* *Chromophobe adenoma of the hypophysis.*" P. F. Morse, M.D.

#### SUMMARY

The case is reported of a man of 52 in whom a gradually developed impotence, feminine pubic hair distribution and gynecomastia are evident. A skiagram gave evidence of a large pituitary tumor. This at autopsy was found to be a chromophobe adenoma of the hypophysis.

# DYSTROPHIA ADIPOSEGENITALIS, WITH ATYPICAL RETINITIS PIGMENTOSA, MENTAL DEFICIENCY, AND POLYDACTYLISM

(The Laurence-Moon-Biedl Syndrome)

Report of a Case.

H. LISSER, A.B., M.D.

SAN FRANCISCO

Laurence and Moon (1) in 1866 reported a family group of four of eight brothers and sisters, who showed retinitis pigmentosa, adiposity, genital dystrophy and mental deficiency; three of these likewise showed imperfections of bony and muscular development leading to defective gait; there was no sign of rickets, of scrofula, nor of syphilis. "The author recognized that the retinal changes were but part of a general developmental failure and that, especially in view of the mental condition, these persons could be, not inaptly, compared to cretins" (quoted from article by Solis-Cohen and Weiss).

Biedl (2) in 1922 and Raab in 1924 (3) report another family of six living boys and girls of healthy parents, two of whom (a brother and a sister) showed atypical retinitis pigmentosa, adiposity, genital dystrophy, polydactylism and mental deficiency. Two others of the family who died in infancy showed polydactylism. Assuming that these might have developed the full syndrome had they lived, Solis-Cohen and Weiss comment upon the remarkable parallel of four healthy and four affected children in this group, in that of Laurence and Moon, and in the group recently reported by themselves.

Biedl refers to an observation in the ophthalmological literature by Bardet (1920), who describes a syndrome composed of infantile adiposity, polydactylism and retinitis pigmentosa, and reported one case. De Schweinitz (4) mentions three cases in which he noted the association of pigmentary degeneration of the retina with pituitary diseases and polydactylism. Engelbach, in a personal communication to Solis-Cohen, states that he has seen two cases of this syndrome.

Solis-Cohen and Weiss in 1925 (5) report four of eight brothers and sisters of Italian parentage who exhibited marked adiposity with mental deficiency, genital dystrophy, and atypical retinitis pigmentosa (with diminution of vision); two of the abnormal children also showed polydactylism. The fat distribution was largely of the girdle, mons and mammary type. No anomaly of osseous development was found as far as the sella turcica and sella region were concerned. Sugar-tolerance tests did not indicate pituitary disease; basal metabolism was below normal in three of the children; Wassermann tests were negative in all the children and the

\*Presented at the meeting of The Pacific Coast Oto-Ophthalmological Society, Salt Lake City, July 1-2, 1929.

parents. The thyroid glands appeared to be normal. The poor vision was first noticed at 10, 13, 15 and 16 years respectively. Height, temperature, pulse, respiration, urinalysis, blood pressure and blood count were uniformly normal.

The literature up to April, 1925, has contained reports of twenty cases of this extraordinary syndrome. It is possible that an exhaustive search might uncover a few more instances. It would seem justifiable to regard this distinctive clinical complex as a pathological entity. Solis-Cohen and Weiss, who have had opportunity to reflect on the theories of Biedl and Raab and others, reserve their opinion and await the progress of future research respecting a congenital pituitary deficiency or a congenital defect of trophic centers in the hypothalamus as the pathogenetic factor in this disease.

It so happened that one morning an orthopedic colleague requested me to see an obese girl, whose osteomyelitis he was treating. On the way up to the ward he added that the little patient was almost blind. This elicited my interest and I was already picturing the possibility of a chromophobe adenoma of the hypophysis. Soon after examination was begun this suspicion was abandoned and in its place there came to my mind the rare syndrome described in the preceding paragraphs. The occasion for this change of front was the finding of supernumerary toes. I immediately went in search of the university ophthalmologist and the picture was completed when he reported the fundi as characteristic of atypical retinitis pigmentosa.

#### CASE REPORT

In view of the great rarity of this extraordinary syndrome the following case is herewith recorded:

I. R., aged 8, Spanish, U. C. H., Nos. 48189, 48760, and 49343.

Inquiry into the family history revealed that one maternal uncle had six fingers on one hand. The immediate family consisted of seven brothers and sisters, two of whom died at thirteen and eighteen months respectively. The brother who died at eighteen months of age had six toes on each foot. The three living sisters and one brother of the patient, ranging in age from four months to seven years, seemed to be normal from all accounts, though we had no opportunity of examining them. The family resided at a considerable distance from San Francisco.

It was stated that the patient underwent a normal birth and an uneventful infancy except for two attacks of pneumonia, two months apart, at around one year of age. It was related "that the baby was stuporous for seven days during the second attack." It was shortly after this that the mother first noticed defective vision, a "cross-eyed" appearance, and the first evidence of mental retardation. The girl had always been stout. Otherwise the past history was entirely negative. A physician had examined the eyes when the girl was six years old and stated that "the nerves were involved."

When the patient was seven and one half years of age an abscess appeared at the right shoulder. It was this disturbance that brought the patient to the hospital. X-ray showed an osteomyelitis of the right humerus which was appropriately treated. No further mention will be made of this since it has no relation to the syndrome to be described.

As may be noted in the photograph (Fig. 1), the patient was quite obese, the adiposity being of the so-called "pituitary type." Fig. 2 reveals the supernumerary toes. It was noticed that she walked with difficulty, bumping into things, and that she followed a person apparently by sound rather than sight;



when fed she did not open her mouth until food touched her lips; she made no attempt to look forward toward the spoken voice; she never uttered any sentences, only an occasional Spanish word. It was difficult to estimate her mental age since the child did not understand English, but our psychiatrist, Doctor Olga Bridgman, concluded that her mental age was probably less than two years, a retardation of six years; probable idiocy, necessitating permanent custodial care. The child was cleanly in her habits and had perfect sphincter control. Her inability to see made her unnecessarily fearful so that she yelled loudly when any attempt was made to examine her.

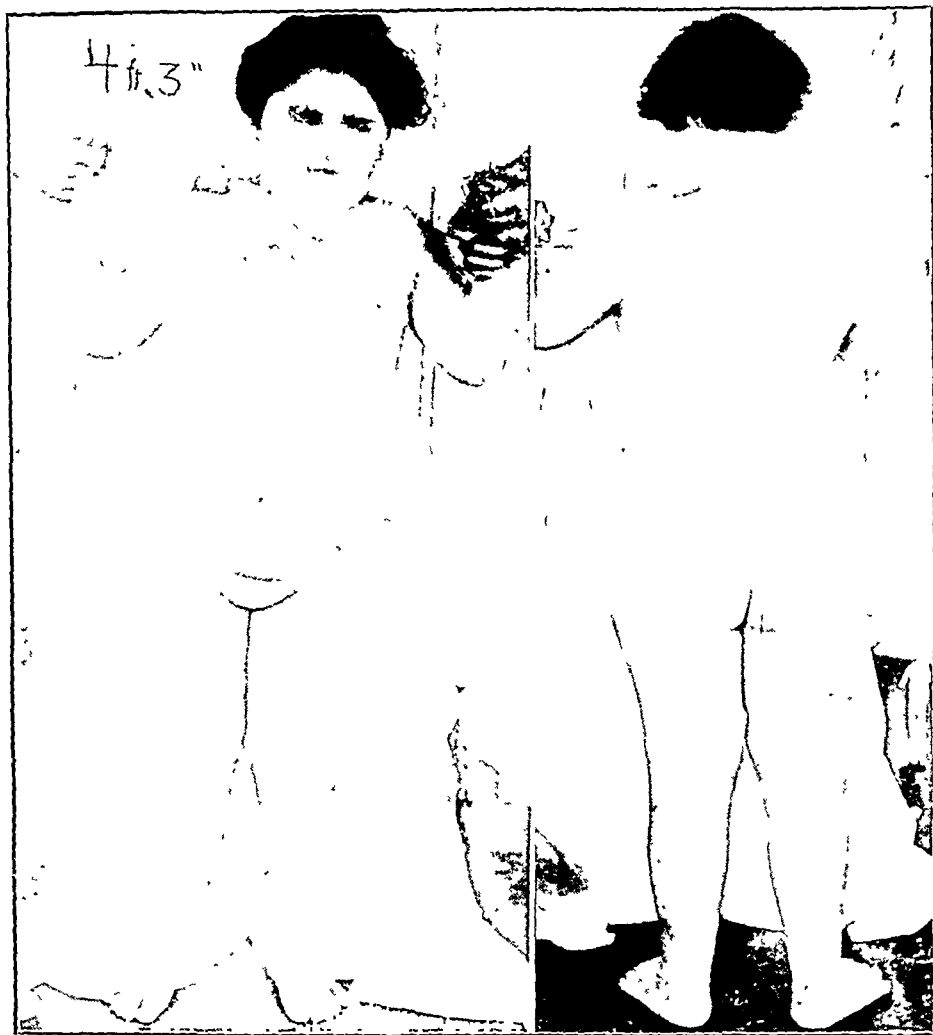


Figure 1

Roentgenogram of her chest did not reveal any thymus enlargement; the heart and lungs appeared normal. Roentgenograms were taken to determine her bone age and it was concluded that ossification lay between seven and nine years of age; nearer seven. Roentgenogram of the skull revealed no abnormality; the sella turcica was normal. Routine examinations of the urine and blood were normal. The Wassermann test was negative. Her blood-serum calcium was 10.4 mgm. per 100 cc. (normal). Glucose tolerance gave the following values: Fasting, .090 per cent;  $\frac{1}{2}$  hour after glucose, .170 per cent;  $1\frac{1}{2}$  hours after glucose, .105 per cent.

Neurological examination was negative except for the second, third and seventh cranial nerves. The latter was thought involved because of slight facial asymmetry.

I am indebted to Doctors Cordes and Horner for the following report of her

eyes: "Left eye is divergent and child looks habitually to the left. She is aware of a flashlight when brought near to her, although she does not follow it with her eyes (light perception only). The eyes make typical searching nystagmoid movements. Under anesthetic and dilatation the media are clear. The right disc is somewhat pale. Its edges are sharp. The fundus vessels are slightly smaller than normal. Some of them bear whitish streaks along their course across the disc. The retina is unusual. A grayish reflex or sheen is quite remarkable. Myriads of very small grayish dots appear throughout the retina except in the macular area. The dots are not clean cut but are round and of the same color, although size may vary from minute to the size of a primary retinal vessel. They are in no place surrounded by pigment. Throughout the fundus but particularly in periphery and mid-periphery are occasional elongated spider leg shaped threads of pigment. They occur often along vessels and when in

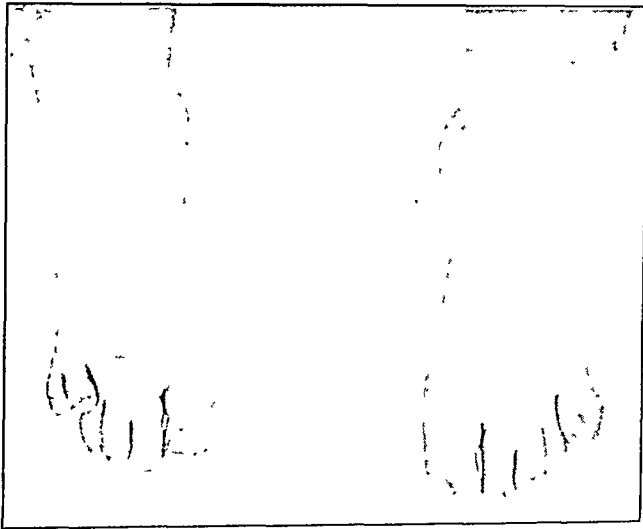


Figure 2

contact cover the vessel (that is, anterior to them). They branch occasionally but are usually in strands. The macular area is clear. Similar findings were noted in the right eye.

*Discussion:* This is a retinitis associated with retinal atrophy, blindness, whitish dots and pigment proliferation. The lesions are in retina and *not* choroid (i.e., not choroiditis). The whitish dots belong to those of retinitis punctata albicans but the pigment is not punctate but strand-like.

*Diagnosis:* The case is one of retinitis sharing features of atypical retinitis pigmentosa and a closely associated type retinitis punctata albicans.

The *prognosis* is absolutely bad. No improvement can be expected and vision may even get worse.

Addendum: Since the above report was written two articles have appeared, one by Beck in a recent issue of "Endocrinology," and another in the German journal, "Endokrinologie," recording other instances of this syndrome.

#### CONCLUSION

A case of the extremely rare Laurence-Moon-Biedl Syndrome has been recorded. The writer has no original theories as to the etiology of this bizarre symptom complex and nothing to add to the excellent article of Solis-Cohen and Weiss, to which the reader is referred for further details.

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# THE EFFECT OF ADRENALINE ON THE HEART OF THE CHICK EMBRYO

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## INTRODUCTION

The influence of various medicaments upon the heart has been widely studied. The earlier experiments for the most part dealt with the hearts of adult animals. So far as we are aware few similar studies have been made on the embryonic heart. It seemed desirable, therefore, to make such a study, using adrenaline as the test substance. During the course of our studies Doctor Tuji of Kioto published the results of a similar investigation which were not, however, entirely in accordance with ours.

We have studied the action of adrenaline on the embryonic chick heart and on strip preparations of it at different stages of development. The hearts were removed, kept in warm Ringer's solution and tested in the same solution.

*The first appearance of automatic movements in the embryonic chick heart:* Since the time of Aristotle the beat of the embryonic chick heart has frequently been observed. The period at which this is first evident, however, has been quite differently reported by different observers. Harvey noted that the heart beat could be detected with careful observation at the end of the third day and easily on the fourth day of embryonic development. Aldrovandus found two beating structures in the 4-day embryo, one in the heart and one in the liver. Later observers have noted the first appearance of heart beats in the chick embryo at the following ages (in hours).

Haller .....	45
Prevost and Dumas.....	36-39
v. Baer .....	48
Carpenter .....	38-40
Wernicke .....	46
Laborde and Laveran.....	26
Preyer .....	36
Ohara .....	33-34
Fujii .....	45

This last author saw no case of appearance of beats earlier than the 40th hour. In our researches the heart beat has been seen in one experimental case as early as the 28th hour, but in most cases only after 33 to 35 hours of incubation. As we see, then, the time of the first beating occurs at a variable period. Some of the conditioning factors are temperature of incubation, kind of egg, climate, etc. Indeed, in our single observa-

tion of a heart beating at the 28th hour the time was summer and development had probably begun already before the egg was put into the incubator. Oliviero Olivo noted that the first heart beat ordinarily occurs when nine somites have been differentiated. He found that at this time no nerve fibers have yet penetrated the heart. Our observations confirm the fact that the first heart beat never precedes the appearance of the 9th somite.

It is to be noted that if, in a given experiment, no heart beat is to be seen with the embryo in situ it should be removed to warm Ringer's solution. Ordinarily, the extirpated heart begins to beat within a few minutes but it persists not more than twenty minutes. The heart beat persists especially long in the third and fourth days of incubation, hence, this age is favorable for experimental purposes. The better activity of the isolated heart as compared with that in situ is perhaps to be ascribed to a depressing influence of body metabolites as previously emphasized by Ohara. Our own observations have been made only on extirpated hearts.

*Heart strip preparations:* According to Kuliabko in the normal heart cycle arrest occurs at different times in different parts: First in the left ventricle, then in the right ventricle and in both auricles and last at the mouths of the great veins in the right auricle. The next beat courses over the heart in the same order. Fano observed movements in small bits of isolated heart tissue of 2-3 day embryos. He determined that the tissue from around the mouths of the great veins beat with normal frequency after removal, whereas, other parts came to a standstill. Later, these parts began to beat but at a diminished rate. Fano ascribed these differences to the fact that the auricle has strongly developed automaticity and weak irritability, whereas, in the ventricle the conditions are reversed. This observation we have confirmed. The frequency diminishes as a rule after isolation of the strips.

#### METHODS

*Material and incubation:* The eggs were obtained fresh from a nearby poultry farm. They were incubated at 38° C. Ventilation was carefully watched. Incubation was reckoned from the time of placing the egg in the incubator.

*Heart extirpation:* The embryo was removed through a window in the shell made by scissors and placed in Ringer's solution at 38-39°. Either the whole heart was used for subsequent experiments or heart strips were prepared.

*Heart strips:* The heart of a three-day embryo consists of merely a small tube from which only two strips can be prepared, namely, from the region of the mouths of the great veins and from the chamber region. This is true also of the four-day embryo. From the fifth to the seventh day, however, a third preparation can be made from the tip of the heart.

*Apparatus:* A ten centimeter container is half filled with Ringer's solution. This is then placed in a larger container filled with warm water.

The temperature of the Ringer's solution is maintained at 37° C. by the addition of warm water to the outer container as needed. The Ringer's solution is copiously supplied with warm oxygen. To avoid any injurious effect of the oxygen blast it is directed by means of a small glass plate which serves as a dividing wall between the test objects. The heart or strip preparation is observed through a microscope.

*Procedures:* Upon introduction into the Ringer's solution the heart preparation at first beats irregularly. This is succeeded by a regular rate whereupon the experimentation can begin. Adrenalin is introduced by drops along the side of the container as far as possible from the preparation. The frequency of beats is then determined at the end of 30 seconds and at intervals to the end of 10 minutes. Pieces that beat irregularly are discarded. The adrenalin chloride of the Sankio Compound, supplied in ampules for injection, is used. This is preserved with chloretone in one-half per cent concentration. The adrenalin is diluted ten-fold with distilled water warmed to 37° C. and introduced with a fine pipette. Fifty drops of this solution make 1 cc. and if 1 drop is added to 5 cc. of Ringer's solution a concentration of 0.0000392 per cent of adrenalin is secured. Either Locke's or Ringer's solution can be used as nutrient medium. We have employed a mixture worked out by Dr. Okuda, consisting of:

Sodium bicarbonate	-	0.01%
Potassium chloride	- -	0.01%
Calcium chloride	- - -	0.02%
Sodium chloride	- - -	0.90%

### III. EXPERIMENTAL RESULTS

#### *A—The influence of adrenalin on the extirpated heart at different stages of development.*

1. *At 29-40 hour stage:* At this stage adrenalin causes a clean cut increase in frequency and in strength of contraction. The effect is short lasting. The increase in frequency ranges from 1:1.09 to 1:1.92, the average being 1:1.49 (See table 1).

2. *At 41-50 hour stage:* The reaction at this stage is similar to that just described. The relative frequency before and after adrenalin administration varies between 1:1.11 and 1:1.94, averaging 1:1.43 (See table 2).

3. *At 51-60 hour stage:* The effect is, with one exception, the same, by and large, as above. The effect comes on more slowly, however, and persists longer than in the younger preparations. The range at this stage is from 1:1.11 to 1:1.60, the average being 1:1.46 (See table 3).

4. *At 61-70 hour stage:* The effect on frequency is somewhat less and the duration is somewhat more prolonged. The range is from 1:1.04 to 1:1.40, averaging 1:1.19 (Table 4).

5. *At 71-80 hour stage:* Here there is an increased effect and longer persistence. The range is 1:1.10 to 1:1.58, averaging 1:1.31 (Table 5).

6. *At 81-90 hour stage:* The accelerating effect is greater here than in the foregoing. The range is from 1:1.26 to 1:1.72, the average being 1:1.48 (Table 6).

7. *At 91-100 hour stage:* At this stage we have observed the most marked effect of adrenaline, as regards both frequency and contraction. The range is from 1:1.13 to 1:2.22, averaging 1:1.53 (Table 8).

8. *At 101-110 hour stage:* The effect of adrenaline is still evident but weaker. The increase in frequency is comparable to that of the earlier stages and the range is from 1:1.24 to 1:1.65, averaging 1:1.47.

9. *At 111-130 hour stage:* The effect is still weaker, being comparable to that of the 71 to 80 hour stage. The range is 1:1.22 to 1:2.11, averaging 1:1.36 (Table 9).

10. *At 140-150 hour stage:* The effect is still easily seen but weak and transient. The range is from 1:1.12 to 1:1.46, the average being 1:1.28 (Table 10).

*B—The effect of adrenaline on heart strips at different stages of development.*

1. *3-day stage:*

*Sinus preparations:* After the addition of the adrenaline generally within a minute the increase of the heart rate is noted. The reaction persists about four minutes, after which the rate returns gradually to normal. The range is from 1:1.11 to 1:1.72, averaging 1:1.30 (Table 11).

*Ventricle and apex strips:* An increase in frequency and height of contraction is observed. The effect is only transitory, the original condition being regained in 5 to 9 minutes. The range is from 1:1.67 to 1:3.75, averaging 1:2.56 (Table 12).

2. *4-day stage:*

*Sinus preparations:* Increase in frequency and height is again noted, the range being from 1:1.2 to 1:2.49, averaging 1:1.33 (Table 13).

*Ventricle and apex strips:* The effect is like that in the 3-day stage except weaker, the range being 1:1.10 to 1:2.70, averaging 1:1.56 (Table 14).

3. *5-day stage:*

*Sinus preparations:* The reaction is transitory, both frequency and contraction being affected. The range is from 1:1.37 to 1:2.10, averaging 1:1.61 (Table 15).

*Ventricle preparations:* After two to three minutes a transient decrease of frequency occurs. The rate then gradually returns to normal. The range is from 1:0.32 to 1:0.17, averaging 1:0.46 (Table 16).

#### 4. 6-day stage:

*Sinus preparations:* A transient increase in frequency and contraction occurs, ranging from 1:1.25 to 1:1.75, averaging 1:1.45 (Table 17).

*Ventricle preparations:* The reaction is an initial decrease in frequency which gradually disappears. The range is from 1:0.34 to 1:0.78, averaging 1:0.53 (Table 18).

*Apex preparations:* Only decrease in frequency is seen; this gradually vanishes. The range is from 1:0.28 to 1:0.70, averaging 1:0.44 (Table 19).

#### 5. 7-day stage:

*Sinus preparations:* An increase in frequency and strength of contraction occurs ranging from 1:1.12 to 1:1.66, averaging 1:1.22 (Table 20).

*Ventricle preparations:* The decrease in frequency is notably more marked, ranging from 1:0.42 to 1:0.86 and averaging 1:0.61 (Table 21).

*Apex preparations:* The effect is similar to that in younger preparations, ranging from 1:0.24 to 1:0.89, averaging 1:0.57 (Table 22).

### DISCUSSION

The results of these experiments show that the automotility of the heart of the chick embryo is evident as early as the 28th hour, but on the average the period is from 33 to 35 hours after the beginning of incubation. This period synchronizes with the appearance of the 9th somite, as Oliviero Olivo has noted. Ordinarily, if one dissects out a heart that has already begun automatic beating and transfers it to warm oxygenated Ringer's solution it continues to beat. The action of adrenaline on the entire extirpated heart is always an increase in frequency regardless of the stage of development.

According to Fujii, the heart does not give any particular reaction to adrenalin in concentration of 0.00002 to 0.001 per cent much earlier than 48 hours after the beginning of incubation, and even on the 4th day of incubation it reacts either lightly or not at all. At the end of the 4th day the stimulating effect of adrenaline is established.

According to our observations throughout the period of 29 to 180 hours of incubation, the heart reacts to adrenaline in concentration of 0.000039 per cent. The reaction is a clean cut increase of frequency and strength of contraction. An explanation of the discrepancy cannot now be offered.

The effect of adrenaline on the heart rate is weakest between the 61st and 70th hours of incubation and strongest between the 91st and 100th hours. According to Oliviero Olivo, at the time heart movements begin nerve fibriles in the heart cannot be seen, hence the heart beat is purely myogenic. His was able to demonstrate the presence of ganglion cells first on the 6th day of incubation. We have frequently confirmed this.

These observations raise the question how the effect of adrenaline on the embryonic chick heart is brought about. According to Kuré adrenaline acts *not only* on the myoneural junctions but on the heart muscle itself. Morishima likewise demonstrated the direct action of adrenaline on the heart muscle by sectioning the sympathetic inflow and allowing the terminals to degenerate. From these facts we reach the conclusion that adrenaline exerts a direct effect on the heart muscle. Otherwise, we must assume that there are nerve-like structures in the embryonal cells which give this reaction, although in a less pronounced way.

By the investigations with strip preparations it is shown that the tissue at the mouths of the great veins without exception show an increase in frequency and strength of contraction. Such variations as appear are only in the degree of reaction. The greatest frequency is noted at about the 120th hour of incubation. These findings are by no means surprising, for the effect of adrenaline on the heart and on the sinus derivatives at the mouths of the great veins must necessarily be the same.

Interesting are the somewhat less striking results with preparations from the ventricle or apex of the heart. These preparations show, up to the third day of incubation, a strong increase in frequency. The reaction is then reversed as age increases and at the fifth day the frequency, after the application of adrenaline, falls below the normal.

These results coincide with those of Funada. Using preparations of the post-embryonic heart, he found also that adrenaline caused an increase in the contraction and a decrease in the frequency. He noted only a weak effect on auricle strips. We, on the contrary, got a clear cut effect with strip preparation from the region of the mouths of the great veins, which tissue is comparable with that of the auricle.

#### CONCLUSIONS

1. Experiments with chick embryos have shown that adrenaline causes an increase in the frequency and contraction of heart preparations without regard to stage of development.

2. Amount of acceleration varies with the stage of development, being weakest at the 61st to 70th hours of incubation and strongest at the 91st to 100th hours.

3. The effect is always transitory.

4. Heart strip preparations from the apex region react to adrenaline by decrease of frequency and height of contraction.

5. The course of the reaction corresponds to that of heart preparations in general.

6. Ventricular strip preparations are also stimulated by adrenaline. From the 5th to 7th day of incubation, however, a decrease in the frequency and an increase in the contractions is to be observed.



7. With apex preparations a decreased frequency but an increased contraction occurs.

8. The effect of adrenaline on the strip preparations is transitory, lasting at most only a few minutes.

9. By and large, the effect of adrenaline on the embryonic heart is the same as that on the post-embryonic with the single exception that preparations from the mouths of the great veins show only increased activity.

10. Certain suggestions are made as to the point of attack of adrenaline.

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TABLE I

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
37	88	96	96	88	...	...	...	...	...	...	...
37	72	114	120	120	100	...	...	...	...	...	...
38	56	100	100	108	100	92	...	...	...	...	...
31, 5	88	96	128	136	128	120	100	92	...	...	...
32	60	80	80	60	...	...	...	...	...	...	...
32	112	144	144	120	112	...	...	...	...	...	...
30	104	152	152	132	128	120	104	...	...	...	...
30, 5	62	88	116	100	...	80	72	62	...	...	...
29	40	48	52	48	40	...	...	...	...	...	...
35	64	64	84	84	80	80	...	...	...	...	...
36	48	56	56	68	56	56	48	...	...	...	...
33	88	92	92	100	92	92	...	88	...	...	...

TABLE II

47	70	136	132	120	112	100	88	72	...	...	...
47	62	80	90	86	82	80	72	66	...	...	...
48	46	72	72	68	62	...	54	...	50	...	...
44	66	106	110	102	100	88	76	72	...	...	...
45	74	88	92	104	100	96	88	76	...	...	...
47	62	88	90	84	80	80	76	72	68	...	...
45	100	120	120	148	136	128	116	108	100	...	...
45	104	108	112	112	...	108	...	...	...	...	...
42	108	112	112	120	...	112	108	...	...	...	...
43	120	136	128	128	120	120	...	...	...	...	...
46	76	84	88	88	84	80	76	...	...	...	...
50	56	84	84	72	64	60	56	...	...	...	...

TABLE III

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
54	76	82	120	120	108	100	92	80	76	...	...
56	88	92	144	136	132	120	112	100	92	...	...
52	128	148	160	156	152	144	132	128	...	...	...
51	144	144	148	160	156	144	...	...	...	...	...
53	88	104	112	128	128	112	108	100	92	...	...
52	80	128	128	120	116	108	108	92	88	...	...
57	100	144	144	144	152	160	152	140	128	...	...

TABLE IV

70	148	156	160	160	156	156	152	148	...	...	...
70	144	152	152	148	148	148	144	...	...	...	...
66	122	...	150	150	146	142	136	128	128	...	...
68	130	144	144	147	...	144	136	132	...	...	...
69, 5	76	80	90	90	88	84	80	76	...	...	...
67	128	168	180	180	180	172	...	...	...	...	...
68	140	160	160	180	192	192	192	192	180	...	...
68, 5	140	160	176	176	168	160	...	...	148	...	...
65	140	140	160	160	148	148	140	...	...	...	...
69	140	160	168	168	168	152	...	...	140	...	...
69	140	172	172	168	160	156	...	...	152	...	...

TABLE V

72	104	140	152	156	156	140	132	...	...	...	...
72	66	72	86	86	84	82	78	...	...	...	...
73	85	100	105	...	...	100	88	...	...	...	...
75	152	160	168	160	160	156	152	...	...	...	...
76	144	160	160	160	160	156	152	...	...	...	...
74	108	160	160	140	124	124	124	...	...	...	...
76, 5	120	120	152	160	156	148	148	...	...	...	...
76, 5	156	164	176	168	168	168	160	...	...	...	...
77	96	100	108	124	112	104	100	...	...	...	...
79	100	100	100	148	148	132	124	...	...	...	...
80	120	128	128	140	132	132	...	120	...	...	...

TABLE VI

85	120	140	164	176	168	140	...	...	...	...	...
87	120	140	160	164	140	132	...	...	...	...	...
84	120	156	172	168	156	136	120	...	...	...	...
85, 5	120	168	172	144	136	128	120	...	...	...	...
86	128	168	168	180	180	180	172	164	...	...	...
84	100	136	168	168	168	140	132	120	...	...	...
88	120	132	152	164	156	148	136	124	...	...	...
89	120	128	168	160	152	144	128	120	...	...	...

TABLE VII

93	76	152	128	104	96	88	84	...	...	...	...
94	80	116	88	...	...	...	...	...	...	...	...
95	144	128	128	100	100	96	96	...	...	...	...
96	156	156	156	176	176	160	152	140	...	...	...
96	120	132	132	156	152	140	132	120	...	...	...
98	64	144	80	64	...	...	...	...	...	...	...
98	92	96	104	...	...	...	...	...	...	...	...
99	96	112	108	96	...	...	...	...	...	...	...
100	60	60	68	80	96	80	80	72	...	...	...
100	68	72	80	88	88	76	72	72	68	...	...
100	92	120	144	100	100	100	96	92	...	...	...
92	80	160	176	156	140	132	128	120	100	...	...

TABLE VIII

101	120	172	172	124	120	...	...	...	...	...	...
105	96	148	140	120	116	108	100	...	...	...	...
107	128	128	152	156	156	144	128	...	...	...	...
109	80	80	80	124	128	132	132	120	112	...	...

TABLE IX

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
116	80	92	98	...	...	...	...	...	...	...	...
123	80	100	100	96	80	...	...	...	...	...	...
120	140	160	168	172	168	160	144	...	...	...	...
120	107	144	140	120	120	...	...	...	...	...	...
124	100	112	124	100	...	...	...	...	...	...	...
125	72	128	152	72	...	...	...	...	...	...	...
126	100	128	140	128	100	...	...	...	...	...	...
128	92	108	108	92	...	...	...	...	...	...	...

TABLE X

149	84	100	100	88	84	...	...	...	...	...	...
143	52	76	64	...	...	...	...	...	...	...	...
145	60	84	84	72	60	...	...	...	...	...	...
148	80	100	100	84	80	...	...	...	...	...	...
150	64	80	68	...	...	...	...	...	...	...	...
142	64	72	64	...	...	...	...	...	...	...	...

TABLE XI

54	140	140	160	148	140	...	...	...	...	...	...
54	144	152	160	148	148	144	...	...	...	...	...
52	108	108	108	144	128	128	120	108	...	...	...
53	124	148	164	144	140	128	124	...	...	...	...
53	124	140	160	144	132	124	...	...	...	...	...
52	120	120	136	140	140	152	140	120	...	...	...
53	136	140	156	148	148	140	136	...	...	...	...
54	80	80	80	84	80	80	...	...	...	...	...
49	96	124	124	116	96	...	...	...	...	...	...
48	124	124	160	140	132	124	...	...	...	...	...
47	80	152	156	88	80	...	...	...	...	...	...
46	88	148	136	116	112	88	...	...	...	...	...
46	72	72	84	116	112	104	100	88	72	...	...
50	116	116	120	120	120	116	116	...	...	...	...
51	100	100	136	120	120	116	112	104	104	100	...
52	92	92	128	116	112	112	100	100	96	92	...
54	96	100	104	132	120	116	100	96	...	...	...

TABLE XII

52	72	120	120	100	88	72	...	...	...	...	...
54	56	120	128	112	92	80	68	60	56	...	...
49	44	80	108	68	56	48	44	...	...	...	...
51	32	32	112	88	76	68	64	56	44	...	...
52	52	76	92	92	88	76	64	52	...	...	...
54	32	80	120	108	68	52	40	36	32	...	...
53	38	100	84	64	64	60	40	...	...	...	...
53	48	48	48	92	88	80	60	48	...	...	...

TABLE XIII

76	108	108	120	128	128	124	...	...	...	...	...
76	128	140	148	160	160	148	144	140	...	...	...
76	128	144	152	152	152	148	140	132	128	...	...
79	124	148	144	140	140	132	124	...	...	...	...
77	136	152	152	152	148	140	136	...	...	...	...
77	132	136	140	148	144	140	...	...	...	...	...
78	92	92	92	128	120	100	100	100	92	...	...
78	148	148	148	160	160	152	...	...	...	...	...
78	104	160	156	140	140	132	116	108	104	...	...
76	68	80	84	156	136	128	...	...	...	...	...
76	100	168	160	132	128	120	108	108	100	...	...
77	144	160	168	168	152	144	...	...	...	...	...
77	88	168	136	128	120	112	108	100	...	...	...
77	120	124	124	156	124	120	...	...	...	...	...
75	140	160	160	140	...	...	...	...	...	...	...
75	128	148	180	140	132	132	128	...	...	...	...
76	128	152	176	160	152	148	140	132	128	...	...
74	132	140	152	144	140	...	138	132	...	...	...
74	100	124	168	120	112	108	100	...	...	...	...
74	128	140	160	128	...	...	...	...	...	...	...

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
76	40	40	108	96	96	84	76	72	...	...	...
76	60	80	84	72	64	60	60	...	...	...	...
74	60	68	72	60	60	...	...	...	...	...	...
76	48	48	48	60	56	48	48	...	...	...	...
79	40	40	44	40	40	...	...	...	...	...	...
77	72	80	84	72	...	...	...	...	...	...	...
77	56	64	76	56	...	...	...	...	...	...	...
78	48	85	60	48	48	...	...	...	...	...	...
78	48	60	72	56	56	56	52	52	52	48	...
78	60	120	72	...	...	...	...	...	...	...	...
76	40	100	76	60	52	48	40	...	...	...	...
74	52	52	84	64	60	58	52	...	...	...	...
77	52	56	104	52	...	...	...	...	...	...	...
75	100	104	112	108	108	100	...	...	...	...	...
75	108	140	108	...	...	...	...	...	...	...	...
76	68	80	80	92	88	84	72	68	...	...	...
74	108	116	160	156	148	148	132	120	108	...	...
74	64	68	84	64	...	...	...	...	...	...	...
73	92	96	160	148	132	128	120	108	92	...	...
73	80	132	132	136	136	136	136	120	104	94	...
74	108	124	128	140	120	120	120	108	...	...	...
74	68	68	88	68	...	...	...	...	...	...	...

100	120	180	160	120	...	...	...	...	...	...	...
100	80	92	92	100	88	88	88	80	...	...	...
102	80	140	136	120	100	96	88	88	80	...	...
102	72	144	132	108	108	108	100	92	80	76	...
96	64	136	136	108	108	...	...	...	...	...	...
96	128	176	152	128	...	...	...	...	...	...	...
102	108	140	176	180	180	180	176	172	172	...	...
102	100	140	168	160	156	152	140	...	...	...	...
102	124	152	180	160	152	148	140	132	124	...	...
100	120	120	148	140	132	132	128	120	...	...	...
100	112	144	156	148	140	132	120	...	...	...	...
102	108	140	144	160	152	140	132	128	120	...	...

100	64	64	62	24	32	40	...	...	...	...	...
100	64	64	64	48	32	48	...	...	...	...	...
102	48	48	20	20	24	24	28	32	32	...	...
102	68	68	60	52	48	48	52	60	64	68	...
102	76	72	60	24	32	44	60	72	76	...	...
96	80	80	48	52	60	68	72	76	76	80	...
97	72	72	60	32	32	44	68	72	...	...	...
98	76	72	52	36	48	60	72	72	76	...	...
99	60	60	52	32	32	44	56	56	60	...	...

120	56	84	72	56	...	...	...	...	...	...
122	60	60	100	96	96	84	84	80	76	72
122	80	80	116	92	80	...	...	...	...	...
123	80	92	100	...	...	...	...	...	...	...
125	92	92	152	92	...	...	...	...	...	...
124	80	100	100	80	...	...	...	...	...	...
124	100	132	104	...	...	...	...	...	...	...
124	80	140	104	80	...	...	...	...	...	...
124	68	100	84	...	...	...	...	...	...	...
124	72	80	128	116	96	88	80	72	...	...
125	116	128	140	160	152	148	140	132	...	...
125	128	156	164	136	132	128	...	...	...	...
125	112	160	144	136	132	120	116	112	...	...
125	72	88	88	96	72	...	...	...	...	...
125	64	64	64	68	64	...	...	...	...	...
124	100	128	124	...	...	...	...	...	...	...
124	80	100	108	...	...	...	...	...	...	...

TABLE XVIII

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
125	60	60	56	36	40	48	48	60	...	...	...
124	84	60	60	36	32	32	36	40	56	72	...
125	88	88	88	72	76	80	...	...	...	...	...
125	52	52	40	36	44	52	...	...	...	...	...
124	92	92	92	68	72	80	92	...	...	...	...
124	116	104	104	40	48	48	48	56	72	...	...
125	80	80	52	36	40	48	52	60	72	...	...
125	76	76	64	44	52	60	68	72	76	...	...
125	64	64	40	32	36	40	48	56	64	...	...

TABLE XIX

122	60	60	36	28	28	36	48	52	60	...	...
123	80	80	48	44	44	36	37	36	40	56	68
123	76	56	48	48	48	48	44	48	52	60	64
124	64	48	20	24	24	24	28	36	48	52	60
125	52	44	28	24	24	24	28	32	40	52	...
125	68	68	68	32	32	32	28	32	36	44	56
124	68	68	68	52	48	60	72	76	...	...	...
124	76	76	74	40	40	40	48	52	60	68	...
124	76	76	76	36	28	36	40	48	56	60	...
124	64	64	64	28	40	48	52	60	68	72	...
124	76	56	32	40	40	36	36	36	40	48	...
125	88	84	64	40	40	48	56	...	...	...	...
125	56	56	20	36	24	28	36	40	48	56	...
125	80	80	80	20	52	56	64	68	72	76	...
124	76	76	68	44	44	48	52	56	64	68	...
124	68	56	24	44	52	56	56	64	68	...	...
124	68	68	60	48	44	52	64	...	...	...	...
124	64	64	60	44	...	...	...	...	...	...	...

TABLE XX

148	140	144	160	160	156	148	140	...	...	...	...
148	72	76	84	112	112	108	100	...	...	...	...
148	108	112	132	108	...	...	...	...	...	...	...
150	132	140	144	136	136	132	...	...	...	...	...
150	100	100	116	100	...	...	...	...	...	...	...
146	120	140	140	160	148	140	...	...	...	...	...
146	132	148	140	...	...	...	...	...	...	...	...
150	128	140	160	160	144	140	132	128	...	...	...
150	132	140	152	144	140	138	132	...	...	...	...
140	120	120	138	160	152	144	132	128	120	...	...
140	124	140	160	164	152	144	136	124	...	...	...
142	132	148	152	132	...	...	...	...	...	...	...

TABLE XXI

148	88	88	72	52	52	52	56	50	68	72	...
148	64	64	64	36	32	32	36	44	48	56	60
150	92	92	92	64	72	80	84	88	92	...	...
146	80	80	80	60	64	72	76	80	...	...	...
146	88	84	80	60	72	76	88	...	...	...	...
146	84	84	56	64	68	76	80	84	...	...	...
146	76	68	60	32	36	36	72	72	76	...	...
148	60	60	60	52	60	60	...	...	...	...	...
148	92	76	68	60	64	72	76	80	88	92	...
150	96	96	72	48	52	60	68	76	88	96	...
140	76	72	68	36	40	52	60	76	...	...	...
140	80	80	76	52	52	60	68	76	80	...	...

TABLE XXII

Incubation Time, Hours	Initial Rate	After 30 Sec.	After 1 Min.	After 3 Min.	After 4 Min.	After 5 Min.	After 6 Min.	After 7 Min.	After 8 Min.	After 9 Min.	After 10 Min.
148	100	100	96	48	44	40	48	56	64	72	76
148	56	56	56	52	24	32	40	44	48	52	56
148	44	40	37	36	32	28	32	36	40	44	...
148	68	60	56	48	36	40	44	48	56	68	...
150	68	68	52	60	68	...	...	...	...	...	...
150	84	84	42	28	28	36	40	48	56	60	68
150	100	100	88	64	72	84	84	92	100	...	...
150	92	88	60	44	48	48	52	60	64	72	72
146	80	76	72	64	68	68	72	76	80	...	...
146	76	76	76	72	72	72	76	...	...	...	...
146	64	60	52	48	52	60	64	...	...	...	...
148	68	68	44	40	40	44	52	60	68	80	...
150	80	80	64	56	56	60	60	64	72	...	...
150	84	72	48	44	48	56	60	68	72	...	...
150	56	56	32	28	28	36	44	48	56	...	...

# THE INFLUENCE OF SUPRARENAL SUBSTANCE ON MUSCLE AUTOLYSIS *IN VITRO*

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## INTRODUCTION

From the metabolic point of view the data with respect to the suprarenal gland indicate that it is concerned in the catabolic rather than the anabolic phase. This holds for both cortex and medulla. The rôle of medullary activity in carbohydrate mobilization is too well known to need direct citation. The evidence from the cortical side is indirect but significant. Jaffé (1924) observed that thymus involution was retarded by suprarenalectomy, and that thymus regeneration in older animals occurred under like conditions. Hammett (1928) reported acceleration of thymus autolysis *in vitro* when cortical substance was added to the digest.

As far as tissue autolysis is concerned, but little consistency is found in the literature. Izar and Fagiuolo (1916) reported that suprarenal extract had no effect on liver pulp. Kawashima (1910) found no enzymes in extracts of horse suprarenal cortex. Obie (1923) obtained negative results when muscle was digested with epinephrine or suprarenal extract. Yasusade (1926) saw no influence of epinephrine on phosphoric acid liberations on autolysis of muscle or liver tissue. On the other hand Gruber (1924) and Hoskins and Durant (1923) consider epinephrine acts as a metabolic catalyst.

In view of these reports and the results of Hammett (1928) it seemed desirable to determine the influence, if any, of suprarenal cortex and medulla on muscle tissue autolysis *in vitro*.

In the work described here fresh cortical or fresh medullary tissue was added to fresh muscle tissue of the same animal. The procedure was as follows.

## PROCEDURE.

Guinea pigs were killed with ether. Muscle tissue was removed and pulped in a meat grinder. Twelve approximately equal amounts (2 to 3 gms.) of the thoroughly mixed mass were transferred to an equal number of weighing bottles and weighed. Of these 6 were used for controls and 6 for tests. The weighed tissue was moistened with toluene, then ground with fine sand. It was at this point that the bits of cortex or medulla was incorporated into 6 of the muscle tissue samples. While one lot was being ground the others were kept cool in an ice bath. The ground up mass was transferred to a centrifuge tube. To it was added 16 cc. of saline buffered to pH 5.9 with phosphate mixture, and 3 drops of toluene. After thorough

mixing 3 samples containing cortex or medulla, and 3 samples without this addition were incubated at 37° C. for 24 hours. The remaining 6 lots (3 with and 3 without glandular substance) were immediately centrifuged for 10 minutes. To each was added 4 cc. 10 per cent tri-chlor-acetic acid and the mixture again centrifuged. The clear supernatant liquid was then analyzed for  $\text{NH}_2\text{-N}$  according to the method of Van Slyke (1912). The incubated samples were similarly treated.

There was thus had for comparison the  $\text{NH}_2\text{-N}$ , in triplicate, of muscle tissue with and without suprarenal cortex or medulla, before and after incubation.

The phosphorous in the extract was determined according to Fiske and Subbarow (1925). This was done on separate material but treated exactly as described up to the point of precipitation. Here 20 cc. of 10 per cent tri-chlor-acetic acid was added to 5 cc. of the muscle extract and filtered. Ten cc. of the filtrate was used for analysis.

### RESULTS

In table 1 are given the figures for initial and terminal  $\text{NH}_2\text{-N}$  values, the percentage increase on incubation, and the difference of the increase of

TABLE I

THE AUTOLYTIC PRODUCTION OF  $\text{NH}_2\text{-N}$  IN MUSCLE TISSUE UNDER THE INFLUENCE OF SUPRARENAL CORTEX AND MEDULLA.

Expt.	NH <sub>2</sub> -N per cent per gram tissue				Percentage Increase		T-C
	Initial		Terminal		Contl.	Test	
	Contl.	Test	Contl.	Test			
CORTEX							
1.	0.0472	0.0386	0.1097	0.0931	132.4	141.2	8.8
2.	0.0596	0.0502	0.1186	0.1120	99.0	123.1	24.1
3.	0.0640	0.0657	0.1267	0.1259	98.0	91.6	-6.4
4.	0.0573	0.0548	0.1000	0.1141	74.5	108.2	33.7
5.	0.0601	0.0624	0.1038	0.1110	72.7	77.9	5.2
6.	0.0534	0.0554	0.1252	0.1267	134.5	128.7	-5.8
7.	0.0591	0.0613	0.1207	0.1258	104.2	105.2	1.0
8.	0.0619	0.0607	0.1162	0.1187	87.7	95.6	7.9
MEDULLA							
1.	0.0574	0.0584	0.0853	0.0865	48.6	48.1	-0.5
2.	0.0512	0.0550	0.0855	0.0981	67.0	78.4	11.4
3.	0.0534	0.0456	0.0714	0.0842	33.7	84.7	51.0
4.	0.0600	0.0481	0.0694	0.0995	15.7	106.9	91.2
5.	0.0430	0.0438	0.1025	0.1128	138.4	157.5	19.1
6.	0.0480	0.0517	0.0766	0.1002	59.6	93.8	34.2
7.	0.0409	0.0397	0.0859	0.0956	110.0	140.8	30.8
8.	0.0492	0.0458	0.0816	0.0754	65.9	64.6	-1.3

the tests from the controls for both cortex and medulla. In table 2 the like values for phosphorus are given. It is to be noted that the value for each experiment represents the average of determinations on 3 separate samples of muscle tissue; not determinations on 3 aliquots of extract from a single weighed muscle specimen.



The results show that autolysis of muscle tissue proteins giving rise to amino-acids is increased on the average by 8.6 per cent when cortical substance is present and by 29.5 per cent when medullary tissue is added. Since the amount of added gland material was too small to give the increase by itself, the conclusion is that suprarenal accelerates muscle protein autolysis *in vitro*. Whether or not the result with cortex is attributable to possible contamination with medulla is undeterminable from these experiments. The only significant thing that can be said with security is that the evidence is consistent with the idea that the suprarenal may be a participant in the catabolic phase of nitrogen metabolism.

The source of the inorganic phosphorous increase in studies of this nature is indeterminate. There is a possibility that a large part comes from the hydrolysis of phospho-creatine. Apparently medulla has no influence upon this process. It is possible that cortex has an inhibitory effect as reflected in table 2. Unfortunately it was necessary for me to drop this

TABLE II

THE AUTOLYTIC PRODUCTION OF INORGANIC PHOSPHORUS IN MUSCLE TISSUE UNDER THE INFLUENCE OF SUPRARENAL CORTEX AND MEDULLA.

Expt.	- P per cent per gram tissue				Percentage Increase		C-T
	Initial		Terminal				
	Contl.	Test	Contl.	Test	Contl.	Test	
CORTEX							
1.	0.147	0.167	0.197	0.196	34.0	17.4	16.6
2.	0.164	0.188	0.223	0.228	36.0	21.3	14.7
3.	0.175	0.171	0.206	0.196	17.7	14.6	3.1
4.	0.168	0.174	0.199	0.209	18.5	20.1	-1.6
MEDULLA							
1.	0.181	0.193	0.216	0.226	19.3	17.1	2.2
2.	0.176	0.185	0.214	0.225	21.6	21.6	0.0
3.	0.182	0.189	0.223	0.227	22.5	20.1	2.4
4.	0.189	0.193	0.209	0.213	10.6	10.4	0.2

phase of the work before the point could be established. The figures are merely presented in order that they be on record.

#### SUMMARY AND CONCLUSION

Autolysis of muscle tissue of the guinea pig was studied with regard to the influence of suprarenal substance thereon. It was found that both cortex and medulla accelerate amino-acid production on incubation, the latter more strongly. Similar studies of inorganic phosphorus liberation gave no sure results. The conclusion is that a metabolic rôle of the suprarenal is that of a participant in catabolism.

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# AN ENDOCRINE CONSIDERATION OF RECKLINGHAUSEN'S DISEASE: REPORT OF A CASE WITH ASSOCIATED CHILDHOOD MYXEDEMA

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The simultaneous occurrence of Recklinghausen's disease and endocrine dyscrasia in the same individual has resulted in a discussion of the relationship between the two conditions. Those who have reviewed the literature have arrived at contradictory conclusions. Tucker (1) claims that there is a definite relationship between Recklinghausen's disease and certain endocrine disorders. Levin (2) states that the condition of generalized neurofibromatosis is a clinical entity depending essentially for its etiology upon endocrine dysfunction. Mosbacher (3) infers that the conception of this symptom must be extended to include the simultaneous occurrence of endocrinopathy and to consider all cases in which this is not evident as exceptions. Szondi and Kenedy (4) and Starek (5), who has recently published an extensive review of the entire subject, conclude that while the coincidental advent of both conditions is more than accidental, they are not basically dependent upon one another but upon a common third genetic factor. This view is also held by Dumbrowsky (6), who does not see any causal relationship between Recklinghausen's disease and incretory disorders, since there are cases in which there is no endocrinopathy present and others in which the endocrine dyscrasia appears later. Prange, in Curschmann's monograph on endocrine disorders (7), considers that the pluriglandular insufficiency is only accessory and not in any way causal.

Pende (8) states that two factors are essential for the production of such dystrophies as Recklinghausen's disease: (1) A constitutional factor represented by an abnormality of the endocrine-sympathetic system which may be hereditary; (2) an accidental factor, such as shock, trauma, toxic poison, infection, etc., which through its effect on the endocrine-sympathetic system acts as a stimulus on the embryonal elements. This theory concurs in principle with that of Ewing (9), who considers that the underlying factor in Recklinghausen's disease is a disturbance between the ectoderm and the tissues it enervates, and that under certain exciting conditions the congenital malformation of the ectoderm may develop manifestations of the disease. The consensus of opinion in the literature on the general etiology of neurofibromatosis, without particular reference to the question of endocrine relationship, seems to be that it is of ontogenetic origin, traceable to a developmental anomaly of either the mesoderm or ectoderm or both.

For purposes of orientation, it may be advantageous at this point to briefly consider the important features of generalized neurofibromatosis or Recklinghausen's disease. The first clinical descriptions were published by Kolliker in 1860 and by Virchow in 1863. Recklinghausen in 1882 (10) traced degenerating nerve fibres in several cases and stated that all of the tumors arose from nerve trunks or filaments. His conclusions have been verified by the studies of subsequent investigators.

The disease may have its onset during childhood, remain quiescent for several years and then become reactivated in adult life, or else may be progressive from its inception. The condition may be familial, as shown by Preiser and Davenport (11), who found an incidence of 43.5 per cent in 115 children whose parents were affected with Recklinghausen's disease. Both Starek (5) and Schiff (12) reported its occurrence in three generations. This familial tendency is also present in the incomplete forms as observed by Thiebierge (13), who cites instances of families in which one member showed tumor formation while another displayed pigmentation only.

The cardinal symptoms of the disease are generalized neurofibromatosis, cutaneous pigmentation and mental and psychic alteration. To these may be added cachexia, osseous changes and endocrine dysfunction.

A discussion of the various types of tumor formation included under the general classification of neurofibromatosis will not be attempted here. Suffice it to say that the tumors may be plexiform neuromas, with or without multiple molluscous tumors of the skin, neurofibromata of the nerve trunk or fibroma molluscum. They vary in size from that of a pin point to a goose egg and may occur in any number up to several hundred. The nerves which may be affected are the motor and sensory, the special cerebral with the possible exception of the optic and olfactory, and at times the sympathetic.

Other sites of predilection are the true skin, the subcutaneous tissues and the muscles. At the onset the tumors are soft, but when fully developed are hard and fibrous and may be felt as firm, shot-like, sessile or pedunculated nodules under the skin. They may be discrete or coalesce; if matted together, they give the impression of a strand of cord whose course is discernible as subcutaneous elevations. They may be tender and painful to the touch.

Cutaneous pigmentation consists of diffuse, irregularly distributed patches or sheets varying in color from a cafe au lait to an intense brown, and in size from a pin point to an area which may extend over one-third of an extremity. Light reddish colored areas, naevi, lentigo and freckles may also be present.

Starek thinks that pigmentation is due to either idiopathic degeneration of the germinal layers or to endocrine dysfunction. On the side of an endocrine basis are found many observers, among them Wegelin (14),

Goodhart (15) and Levin (2), who consider it a sign of adrenal insufficiency, while Th. Kocher feels that it is due to thyroid dyscrasia (16).

Mental impairment is so frequently associated with Recklinghausen's disease that many feel that somatic stigmata of degeneration, imbecility, mental aberration and psychic disturbances are integral parts of the complete picture of the disease. Thiebierge (13), Starck (5), Adrian (17), Knoblauch (18) and Speransky (18) have recorded instances of this association.

Incomplete forms with the absence of one or more of the cardinal symptoms have been observed. Thiebierge (13) was the first to describe a type of this disease which is characterized by pigmentation without tumor formation and which is now considered as an incomplete form. Instances of this type have been reported by Herxheimer and Roth (19), Weber (20), Adrian (17), Littlewood (21) and Wise and Eller (22).

Three additional syndromes are considered by Starck (5) as being incomplete forms of Recklinghausen's disease: (1) Leschke syndrome, characterized by cutaneous pigmentation and endocrine dyscrasia with absence of neurofibromata; (2) Laurence-Biedl syndrome, characterized by endocrine dysfunction with absence of both pigmentation and neurofibromata; (3) Cerebral Tuberous Sclerosis (Tuberosa Gehirnsklerose), characterized by cutaneous pigmentation, cutaneous fibromata and tumors of cerebral cortex.

E. Leschke (23), under the term of dystrophia pigmentosa, described a symptom complex occurring in individuals exhibiting the incomplete type of Recklinghausen's disease in association with an endogenous pluriglandular insufficiency. The clinical picture of Leschke's syndrome consists of arrested growth with physical and mental infantilism and increased cutaneous pigmentation in the form of cafe au lait spots, naevi and freckles. Endocrine dysfunction is expressed in obesity, genital hypoplasia, impaired carbohydrate metabolism, low blood pressure, hypotonia and asthenia. Giantism or signs of hypothyroidism may also be present. Vegetative nervous system changes are evidenced by increased irritability of the sympathetic and parasympathetic systems. Instances of this syndrome have been observed by Leschke (24), Ulmann (24), Hoffmann (25), Galant (26), and Barber and Shaw (27).

Biedl in 1922 (28) described a form of cerebral obesity which had previously been observed and reported by Laurence and Moon in 1866 (29), the predominating symptoms of which are : (1) Dystrophy adiposa genitalis, expressed in obesity and genital hypoplasia; (2) congenital maldevelopment, such as retinitis pigmentosa, atresia ani and polydactylitis; (3) skull deformities, as macrocephalus, microcephalus, tower-skull, and asymmetry; (4) mental delinquency.

Solis-Cohen and Weiss (30) reported four cases in 1925, all of the patients showing a reduction of the basal metabolic rate. Bernhardt (31) observed two patients with this syndrome. Both were of the vagotonic type

with normal metabolic rates. The sella turcica was found normal on radiographic studies in both patients. One of the patients showed symptoms of diabetes insipidus. Zondek (32) reported two cases of this type. A simultaneous hypophyseal dyscrasia was reported by Bohn (33).

Tuberous sclerosis of the brain is a condition which is thought to be due to mal-development of the mid-brain (Starck) and is characterized by tumor-like foci in the cerebral cortex and ventricular walls. Other organs may also be studded with multiple sclerotic nodules. The clinical picture consists of neurological and mental aberration, such as epilepsy, idiocy and signs of mid-brain pressure; cutaneous pigmentation, as freckles, naevi, cafe au lait spots and lentigo; cutaneous fibromata on neck and back.

Orzechowski and Nowicki (34) and Pick and Bielschowsky (35) think that a relationship exists between tuberosa sclerosa and Recklinghausen's disease. Schuster (36) observed families in which tuberosa sclerosa occurred in one member and Recklinghausen's disease in another.

While Starck feels that Recklinghausen's disease, Leschke's syndrome, Laurence-Biedl syndrome and tuberosa sclerosa are all expressions of the same ontogenetic mal-development, the majority of investigators do not mention the Laurence-Biedl syndrome nor tuberous sclerosis in this connection (37).

According to Starck (5) the condition of the affected endocrine glands in Recklinghausen's disease falls into one of three groups: (1) A tumor of either the endocrine gland itself or of the surrounding neighborhood producing pressure symptoms, as in tumors of the hypophysis or mid-brain; (2) functional disturbance without anatomical alteration; (3) functional disturbance with anatomical lesions, such as in anomalies.

The glands which have been reported as having been involved are the thyroid, parathyroid, pituitary, adrenals and gonads.

Thyroid dysfunction was frequently encountered. Cretinism was observed by Adrian (17), Strohmeyer (38), Schuh (39) and Ottolia (40). Schiffner (41) reported the occurrence of association with cretinism in two brothers. Andueza's patient was a cretin presenting a neurofibroma in the region of the thyroid (42). Pic and Rebattu (43) and Meige and Feindel (44) reported myxedematous symptoms in their patients. Hypoplasia and hypothyroidism were observed by Dumbrowsky (7) and Roederer (45). The mother of the latter's patient had cutaneous pigmentation. Ehrmann (46) reported two cases, in one of which the thyroid was small and in the other was entirely absent. Thyroid infantilism, pigmentation and neurofibromatosis were found associated by Debove (47). Galant's patient had a combination of Leschke's syndrome, mongolian idiocy and myxedema (26). Hyperthyroidism and goiter were encountered by Hallopeau and Ribot (48) and Bourey and Laignel-Lavastine (49). According to Levin (2), the only case of Recklinghausen's disease associated with parathyroid tetany was reported by Schlesinger (50).

A diagnosis of hypophyseal dysfunction was made on the presence of acromegaly, gigantism, polydipsia, polyuria, and dystrophia adiposa genitalis. Pituitary involvement was observed by Feindel and Froussard (51), Piollet (52), Nicolas and Favre (53), Cushing (54), Wolfsohn and Marcuse (55), Raymond and Alquier (56), Roubinowitsch and de la Sourdier (57), Mann (58), Escher (58), Tucker (1), Barker (58) and Bittdorf (58). De Castro (59) reported the association of a pituitary tumor, acromegaly and Recklinghausen's disease. Lier's patient (60) was a boy of 9 years who presented a typical picture of Froelich's syndrome and a generalized neurofibromatosis. A roentgenographic examination revealed a tumor close to the hypophysis. Spillman (61) reported a case of tumor of the sella turcica.

Adrenal insufficiency was frequently noted. According to Levin, at the time of his report (1921), there were approximately 50 instances in the literature with so-called Addisonian symptoms, an incidence which he felt was too low. A diagnosis of adrenal insufficiency was made in most cases on asthenia, low blood pressure, pigmentation and hypotrichosis. The same investigator reviewed 14 autopsy reports in the literature in which the findings in the glands of internal secretion were included and found adrenal disease in 12.

Gonad association is evidenced by onset of symptoms of Recklinghausen's disease at the time of puberty and their aggravation at the time of menstruation, pregnancy and menopause. An illustrative example of this association is Starck's patient, whose symptoms will be considered later. Levin (2) cites several instances of simultaneous occurrence of gonad dysfunction and Recklinghausen's disease.

Pluriglandular involvement is recorded by Tucker (1), Levin (2), Roederer (45), Mosbacher (3), Castronuovo (62) and Starck (5).

Starck had an excellent opportunity of studying his patient for over 23 years. She first came under his observation at a little above two years of age, presenting a combined picture of rickets, scoliosis, cutaneous pigmentation and severe Basedow's disease. The latter was considered by the author to be the result of psychic trauma. The hyperthyroidism was at its height at the age of 4 years, but in the 9th year coincidental myxedema made its appearance. During childhood, the patient was subject to psychic and nervous disturbances in the form of choreiform movements, outbursts of temper, ferocious habits and incompatibility in regard to her playmates. Her mentality was always below par.

Pituitary disturbance expressed in diabetes insipidus was first noted at the age of 9 years. At 12 years of age, the left arm began to increase in length and at 21 years the right became affected. This increase in size of the extremities is considered as evidence of acromegaly by Starck, who cites several similar instances in the literature (5).

Menstruation began at 14 years of age and continued regularly until the time of pregnancy at 25 years. Pregnancy was accompanied by an

increased functional activity of the thyroid gland, with an increase in the size of the goiter, which had remained quiescent since the age of 9 years. The symptoms of hyperthyroidism receded after the birth of the child. The cutaneous pigmentation, which had been noted early in the history, and a fibroma molluscum, which had appeared at 22 years of age, increased in size and intensity of color during the period of gestation. Neurofibromatosis was first noted at 17 years of age.

#### CASE REPORT

J. S., 9½ years of age, is the only child of parents who are not related by consanguinity, and who do not give any history of neurofibromatosis, mental aberration or cutaneous pigmentation on either side. Born at term, he was only three pounds in weight, puny and cyanotic. He was nursed for three months and then placed on artificial feeding. His developmental history shows retardation in both mental and physical fields: teething began at eighteen months of age, walking at two years and talking at three years.

At the time of his initial visit, April 15, 1926, he presented a typical picture of childhood myxedema, with a round moon face, retrousse nose, dry hair, dry skin, cold extremities, high arched palate, pot belly and umbilical hernia. The tonsils were hypertrophied. There was an incurving of the little finger of each hand. Rachitic condition was manifested by flaring of the ribs and enlarged epiphyses. Fluoroscopic examination of the chest revealed a normal thymic shadow. Roentgenographic study of the sella turcica demonstrated a sella of oval contour, type B (Gordon and Bell classification) (63), and within normal limits as to size. The anterior and middle clinoid processes were well seen and the dorsum sellae well developed. No erosions were found. Examination of the fundi of the eyes showed that the nerve was small, slightly pale in color, and vessels of normal size but tortuous. There was a refractive error for which glasses were prescribed. The Wassermann reaction was negative. He was both underweight and underheight (44 pounds and 43 inches).

His speech was indistinct and his mentality below normal for his physical age. He was friendly, with well developed social tendencies, evidenced by desire to play with other children and his amicable attitude toward strangers.

The hypothyroid condition had been recognized at two years of age and he had been under thyroid treatment since then.

He was placed under intensive treatment, resulting in marked improvement in both physical and mental retardation. An intelligence test performed on Aug. 3, 1927, at the Neurological Institute of New York revealed the following:

"The physical age of the patient is 7 years and 4 months but he attains a mental age of 4 years and 10 months with an intelligence quotient of .66 on the Terman scale. This quotient places him among the high grade morons. He was most friendly and co-operative throughout the entire test. His alert and friendly attitude tends to make one feel that he would test higher than he does. He is very observant and asks questions about things in the room. He responds to praise by putting forth more effort.

"At year IV he has a basal age on the test. With the Vth year series, he succeeded in giving definitions superior to use and carrying out three commissions but fails the remaining tests of the level. With the VIth year tests, he has three successes but fails in reconstruction of mutilated pictures, in the comprehension of simple situations and the naming of coins. His upper limit is reached in the VIIth year."

On June 22, 1927, the first signs of neurofibromatosis were noted in the form of numerous cartilagenous-like nodules giving the impression of buckshot under the skin. These were of fairly general distribution, but more pronounced on the back. Discrete cutaneous pigmentation of light brown color was noted over several parts of the body. A pigmented mole was present on the dorsum of the left foot.

Complete examination on Oct. 22, 1929, revealed the following picture: Weight, 54 pounds; height, 47 inches. The face is not as myxedematous as formerly. The teeth are all of the first set, are well placed and in good condition. The tongue is not hypertrophied. Glasses are still worn.

The skin shows a mottled marble like appearance. Numerous pigmented spots are present ranging in size from a pin point to 2 by 1.2 cm. and in color from light cafe au lait to an intense dark brown with some a light reddish tint. Some of the pigmented areas overlie the subcutaneous nodules, but the majority do not.



Plexiform, cartilagenous-like, fibrous nodules which are movable and sessile are felt in the skin, subcutaneous tissue and muscles. These are both discrete and matted together, giving the impression of strands of knotted cords. Elevations under the skin produced by the nodules may be seen through the skin. There are perhaps hundreds of these small nodules covering the entire body.

There is a hypertrichosis especially pronounced on the skin of the back; the hair is not as dry as formerly.

The abdomen is distended, more so during the past few weeks, but no intra-abdominal tumors are discernible.

The external genitalia are of fair size, both testes are undescended and the scrotum shows a ridge in the median line, producing an appearance not unlike that of the labia majora.

Mentally, he has improved to the point where he is beginning to spell words and speak well, but in a rapid fire manner. He reads signs in the street cars and takes an active interest in his surroundings. He has been masturbating for some time.

For the past five years he has been receiving one grain each of the thyroid extract and pituitary substance three times a day on alternate weeks.

#### COMMENT

The relationship between endocrine disorder and Recklinghausen's disease may be based on one of three possibilities: (1) The endocrine disorder is the fundamental causal factor in the production of the complete picture; (2) the endocrinopathy and the symptomatology of Recklinghausen's disease (generalized neurofibromatosis, cutaneous pigmentation and mental or psychic aberration), while not dependent upon one another, are produced by a common third genetic factor; (3) the simultaneous occurrence of both conditions is accidental without any further significance.

The numerous instances of simultaneous occurrence of both conditions infers an intimate as against an accidental association. Starek's patient, who was under observation for 23 years, affords an opportunity for study of this correlation. At the time of reporting, she presented active signs of both Recklinghausen's disease and of pluriglandular endocrinopathy, the symptoms having appeared in the following chronological order: Pigmentation and hyperthyroidism, myxedema, diabetes insipidus, acromegalic lengthening of the extremities, neurofibromatosis with increase in pigmentation, fibroma molluscum, pregnancy accompanied by an increase in thyroid activity, and in the color and extent of pigmentation and of the fibroma molluscum, and finally birth of a child, to be followed by recession of the hyperthyroidism and increase in size of the fibroma molluscum and in the intensity of the cutaneous pigmentation.

The effects of pregnancy and of other gonad periods on the general endocrine system are too well known to be discussed here. If the cutaneous pigmentation and fibroma molluscum are considered as integral parts of the complete picture of Recklinghausen's disease, then the influence of pregnancy on these two symptoms in this patient were as definite as on the endocrine system. It must be remembered, however, that pigmentation and fibroma molluscum gravidarum may appear during an otherwise normal pregnancy in women who are not suffering from Recklinghausen's disease, and disappear on the culmination of the gestation. Further analysis of

this case shows that while there was a simultaneous change in the general picture of the disease throughout the years, there was evidently no effect noted during pregnancy on the generalized neurofibromatosis.

Conceding that cutaneous pigmentation and cutaneous fibroma are definite and integral parts of the complete symptom complex, and that alterations took place in these two symptoms simultaneously with changes in the endocrine system, it is not definitely proved that the endocrine disorder was at the basis of the entire picture.

This conclusion is also permissible on analyzing the case reports in the literature. Nothing tangible has been advanced to prove conclusively that endocrine dyscrasia is the etiological factor in the causation of this disease. Endocrine association occurs too often perhaps to be merely accidental, but the most that may be assumed is that a third common genetic factor is responsible for both sets of symptoms.

This conclusion, based upon analysis of the clinical pictures described in the literature, is strengthened by the results obtained in this disease by means of organotherapy, even though it may not be justifiable at the present time with our limited knowledge of the endocrines to confirm or rule out endocrinopathy by therapeutic tests. The results obtained with organotherapy are open to interpretation from two viewpoints: the effect on the endocrine dyscrasia and on the disease itself. Unfortunately the scant information to be gleaned from the literature is both conflicting and confusing, due to the failure in some reports to analyze the results from these viewpoints.

This is especially true of instances in which there was an associated Addisonian syndrome of asthenia, low blood pressure, nervousness and gastro-intestinal disturbances in addition to the pigmentation. Amelioration of such symptoms can be considered only as improvement in the adrenal insufficiency and not in the condition of the disease itself. For instance, Revilliod (64) states that he "controlled" symptoms in a patient with an associated Addisonian syndrome to the extent that asthenia disappeared on the administration of adrenal extract and reappeared on its withdrawal. The effect on the tumors is not given. Chauffard and Rodin (65) reported that organotherapy by means of suprarenal extract produced "notable and immediate amelioration" in the signs of suprarenal insufficiency. They also cited cases of Pic and Rebattu (43) and Jullien (66) in which good results were obtained in those symptoms due to suprarenal dyscrasia. Gabriel (67) tried adrenal therapy in two cases of associated osteomalacia and obtained noted improvement in pulse frequency and in the general feeling of well-being, but on the other hand found that the therapy had no remarkable influence on either the osteomalacia or Recklinghausen's disease. Castronuovo (62) instituted adrenin treatment in a patient who had an associated tubercular affection and reported that his patient showed some amelioration of symptoms. This probably consisted of an improvement in

the general condition, as no mention is made of the state of the neurofibromatosis.

The only instance reported in which there was an effect on the fibromatosis was that obtained by Andueza (42). His patient was a cretin who presented neurofibromata in the region of the thyroid, small cutaneous fibromata, cutaneous pigmentation, and signs of thyroid dysfunction. Under ten months of thyroid therapy beneficial results in both endocrine symptoms and in the tumors themselves were noted. The fibroma underwent slow regression in both size and extent, many of them disappearing, and there was an improvement in the endocrine dysfunction.

Adverse results are recorded by Schoonheid (68), who made use of ovarian extract, and Preiser and Davenport (11), who obtained no results with either thyroid or adrenal extract in their patient, who died of progressive asthenia. Curschmann (6) feels that if an associated thyroid insufficiency cannot be improved with thyroid extract, the prognosis does not appear to be hopeful.

In the present case, endocrinopathy was noted early in life, organotherapy was instituted at the age of two years and continued regularly from then on. Signs of neurofibromatosis first appeared at seven years of age, and in spite of intensive treatment the tumor formation has increased in size and extent. Pigmentation, which was not present at the time of his first visit to our clinic, has since appeared with increasing intensity of color and distribution. The endocrinopathies, however, have responded to treatment by an improvement in both mental and physical retardation. An analysis of the results of treatment with thyroid extract extending over a period of seven years demonstrates that this type of treatment had absolutely no effect on either the neurofibromatosis or on the pigmentation, but on the other hand had a beneficial influence on the thyroid dyscrasia.

This would indicate that the existence of the relationship between the two sets of symptoms in this patient was not dependent on the endocrine dyscrasia.

#### SUMMARY AND CONCLUSIONS

A boy of 9½ years of age presents at the time of reporting a picture of typical childhood myxedema, mental retardation, cutaneous pigmentation and generalized, plexiform, subcutaneous neurofibromatosis. The symptoms of thyroid dysfunction were first noted at the age of two years, at which time he was placed on thyroid treatment. In spite of active organotherapy for the next five years, signs of Recklinghausen's disease appeared at the age of seven years. Intensive thyroid treatment has been continued since then.

The treatment with thyroid extract has resulted in an amelioration of the physical and mental retardation due to the thyroid dyscrasia, but has had no effect on the progress of Recklinghausen's disease. On the contrary, the symptoms of the latter have been aggravated during the past year

The late appearance of cutaneous pigmentation and generalized neurofibromatosis in spite of intensive organotherapy over a number of years, and their exaggeration in the face of continued intensive treatment, seems to indicate that the symptoms of Recklinghausen's disease in this patient are not dependent upon endocrine conditions.

An analysis of the literature from an endocrine viewpoint forces the conclusion that nothing definite nor tangible has been advanced to prove that endocrine dyscrasia is the etiological factor in the production of generalized neurofibromatosis. While endocrine association occurs too often to be merely accidental, the most that may be assumed is that a third, common genetic factor is responsible for both sets of symptoms.

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# PITUITRIN HYPERGLYCEMIA AND ITS POSSIBLE VALUE IN DIAGNOSIS

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That hypophyseal secretion has some influence on carbohydrate metabolism is well known. This belief is based on the following data, which are well known to modern pathologists:

*a. In cases of acromegaly (hyperpituitarism) glycosuria is frequent, with or without symptoms of diabetes. Even when there is no spontaneous glycosuria, hyperglycemia and reduction of the carbohydrate tolerance are frequently noted.*

These facts have been confirmed in many clinics. Perhaps the most extensive experiments in this respect are those of Cushing (1), and Davidoff and Cushing (2), whose statistics refer to 100 cases of acromegaly. Yater (3), who studied 79 acromegalic patients, found glycosuria in 10 per cent of them. We have observed 4 glycosuria cases in 26 acromegalic patients (15 per cent), but the figure of 25 per cent given by Bauer (4) seems excessive.

Almost all authors mention spontaneous hyperglycemia in cases of acromegaly, even when there is no glycosuria. We have, however, been unable to confirm this, as is shown by the following table:

TABLE I  
BLOOD SUGAR IN 13 CASES OF ACROMEGALY

Case	Diagnosis	Blood Sugar
I	Typical acromegaly.....	0.77
II	Typical acromegaly and intermittent glycosuria.....	1.33
III	Typical acromegaly.....	1.10
IV	Typical acromegaly.....	0.77
V	Typical acromegaly and intermittent glycosuria.....	1.38
VI	Typical acromegaly.....	1.04
VII	Typical acromegaly.....	0.90
VIII	Typical acromegaly.....	1.00
IX	Typical acromegaly and ovarian atrophy.....	0.83
X	Acromegaloid syndrome.....	0.80
XI	Familial acromegaloid syndrome.....	1.00
XII	Familial acromegaloid syndrome.....	1.00
XIII	Juvenile acromegaloid syndrome.....	0.75

These results can be summarized as follows:

TABLE II

	Hyperglycemia (above 1.2)	Normal Blood Sugar (between 1.2 and 0.8)	Hypoglycemia (below 0.8)
Number of cases.....	2	8	3
Percentages.....	15%	61%	23%

This gives a proportion approximately the same as found when blood sugar is studied in any series of patients of any other kind.

*b. On the other hand, in hypopituitary syndromes, especially in the genital-adiposity of Frölich, diabetes is very rare, and an increase of the carbohydrate tolerance is almost always observed.*

The authors mentioned above, as also many others, have verified this detail sufficiently. As a matter of fact, the tendency towards adiposity of a considerable group of hypopituitary patients has been attributed to this very sluggishness of the carbohydrate metabolism. In my series of 115 hypopituitary patients of all kinds (adiposo-genital syndrome, hypophyseal cachexia, hypophyseal dwarf growth), I have found spontaneous glycosuria in only two cases: a father and son, both affected with typical adiposity, genital insufficiency and hypophyseal tumor. I note that similar cases are mentioned by Shapiro and Kliatshko (5).

*c. The injection of the pituitary extract causes hyperglycemia and sometimes glycosuria.*

This statement is based on the experience of numerous investigators and clinical observers. Reference is made to the literature mentioned in our book (6). Among recent authors we would mention Hines, Leese and Boyd (7), La Barre (8), Nitzescu and Benatato (9), Nitzescu and Ramneato (10), Fritz (11), Clark (12), etc.

We shall see later that our experience in the human clinic warrants our stating that this pituitary hyperglycemia is really an almost constant phenomenon, but of slight intensity, except in a few patients; but the principal interest of this hyperglycemia resides precisely in its selectivity.

*d. Extirpation of the hypophysis raises the carbohydrate tolerance.*

Mention is made in our book (6), which we have already quoted, of the literature dealing with this question. Among recent reports, we would also mention those of the Houssay school (13) and of Pikkat (14), according to whom the hypoglycemia and the resistance to glycosuria is one of the most constant effects of the extirpation of the hypophysis of dogs, after the first few hours during which a transitory glycosuria may appear, and which may be attributed to the narcosis and an incidental lesion of the diencephalic centers. This author differentiates sharply between the humoral hypoglycemic effect, following extirpation of the hypophysis, and the nervous hyperglycemic effect due to the lesion of the neighboring diencephalic centers. For this reason we call attention to his work, as this detail of the glycosuria has created considerable discussion among physiologists as to the glandular or nervous origin of several of the phenomena which follow on the lesion of the hypophyseal region.

*e. The injection of pituitrin opposes and eliminates the hypoglycemic syndrome produced by insuline.*

Ever since the time of Burn's experiments on rabbits (15) and Housay's on dogs, this antagonistic action of pituitrine on insuline hypoglycemia has been known. In the human clinic, our experience shows that this action is much slower and less certain than that of adrenaline, so that from a practical point of view we should not recommend pituitrine to be resorted to as a treatment for hypoglycemic accidents.

*f. The extirpation of the hypophysis increases the organism's sensibility to insuline hypoglycemia.*

Houssay and Magenta (16) were the first to prove this. Whilst a dog deprived of the hypophysis is subject to grave hypoglycemic accidents, and even dies after the injection of the usual doses of insuline, a normal dog is subject neither to great decreases in the glycemia nor to important accidents, when treated with the same dose. Olmstead and Logan (17), Geiling, Campbell and Ishikawa have confirmed these experiments (18).

Our experience in the human clinic does not, however, agree with these experimental data, for in three cases of hypophysial lesion with hypofunctional syndrome, the test of the injection of 10 units of insuline was totally negative. We would state here that this same dose of insuline produces appreciable, and sometimes very intense, accidents in subjects whose defensive system against the hypoglycemia has been modified, as, for instance, addisonians, certain hyperthyroid states, hepatic diseases, etc. (19).

TABLE III  
SENSIBILITY TO INSULINE IN HYPOPITUITARISM

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 10 Units Insuline			Clinical Phenomena
			30'	60'	120'	
I	Hypophysial tumour (adiposogenital syndrome) ..	0.95	0.80	0.80	0.85	Negative
II	Hypophysial tumour (adiposogenital syndrome) ..	0.64	0.60	0.51 <sup>1</sup>	0.70	Slight anxiety
III	Hypophysial tumour (adiposogenital syndrome. Polyuria) .....	1.20	1.00	0.90	0.95	Negative

<sup>1</sup>Patient had some chocolate. We have already published details of this case (20).

In any case, the contradictions observed may be explained by the error, to which we all as physicians are inclined, of comparing data obtained under totally different conditions (organisms of different kinds, spontaneous or experimental syndromes, different techniques used in obtaining the data, etc.).

But we may consider as a definite conclusion that, in the regulation of the carbohydrate metabolism, the hypophysis can be classified in the group of "endocrine factors producing hyperglycemia" together with the suprarenal and thyroid glands, and consequently antagonistic to the "endo-



ocrine factors producing hypoglycemia" represented principally by the pancreas, and perhaps by the gonads and parathyroid glands. Before proceeding, we wish to state that we purposely refer to "the hypophysis" as a single organ, although it is probable that each of its three portions exercise different endocrine functions, yet, as Biedl (21) has remarked, in practice we have not yet adequate data for attributing specifically to the various parts the phenomena which we observe in the human clinic.

As we have stated previously, our experience has shown that the hyperglycemic effect—rarely glycosuric—of the hypophysis extract on the human organism is frequent (but not absolutely constant) and its intensity varies according to the different pathological conditions. Also the period of appearance and development of this hyperglycemia varies in each case. In order to determine these details with precision, we have established a clinical test which consists in determining the blood sugar with the patient fasting, and then at intervals of 30, 60 and 90 minutes after an injection of 2 cc. of a hypophysial extract, which was always the same and was tested and proved active. Our previous experience with normal subjects has shown that under these circumstances the full development of the post-pituitary glycemia curve, and consequently the pathological variations, can be faithfully observed.

In all cases we have followed the technique of Folin and Wu.

The number of subjects observed, and of service for our object, was 44. The results obtained are set forth in the following tables:

TABLE IV  
NORMAL ADULTS

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc Hypophysial Extract		
			30'	60'	90' After
I		0 85	0 92	0 95	0 92
II		0 95	0 98	0 93	0 95
III		0 91	0 94	0 91	0 90
VI		0.80	0.90	0 83	0 81
V		0 90	0 96	0 95	0 90
VI		0 82	0 85	0 82	0 82

TABLE V  
DIABETES MELLITUS

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc Hypophysial Extract		
			30'	60'	90' After
I	Severe diabetes...	2 24	2 34	2 32	2 24
II	Severe diabetes...	2 70	2 90	2 84	2 84
III	Slight diabetes....	1 90	2.10	1 95	1 95
IV	Slight diabetes....	1 80	1 80	1 83	1.80
V	Slight diabetes....	1.55	1 80	1 80	1.56
VI	Medium diabetes..	1 80	1 83	1 80	1 90

TABLE VI  
DIABETES INSIPIDUS

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	No hypophysial symptoms.....	1.12	1.12	1.16	1.16
II	No hypophysial symptoms.....	1.50	1.60	1.60	1.58
III	No hypophysial symptoms.....	1.50	1.68	1.57	1.57
IV	No hypophysial symptoms.....	1.03	1.11	1.20	1.15
V	No hypophysial symptoms.....	1.10	1.19	1.19	1.18

TABLE VII  
TYPICAL ACROMEGALY

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Typical acromegaly.....	0.77	1.20	0.96	0.90
II	Acrom. and intermittent glyc.....	1.33	1.33	1.50	1.79
III	Typical acromegaly.....	1.10	1.25	1.34	1.33
IV	Typical acromegaly.....	0.77	1.10	0.97	0.85
V	Acrom. and intermittent glyc.....	1.38	1.79	1.78	1.78
VI	Typical acromegaly.....	1.04	1.20	1.27	1.33
VII	Typical acromegaly.....	0.90	0.99	1.28	1.35
VIII	Typical acromegaly.....	1.00	1.00	1.28	1.35
IX	Acrom. and ovarian insufficiency.....	0.83	0.82	0.82	0.81

TABLE VIII  
HYPERPITUITARISM

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Acromegaloid syndrome.....	0.80	0.96	0.95	0.90
II	Acromegaloid syndrome.....	1.00	1.05	1.06	1.34
III	Acromegaloid syndrome.....	1.00	1.00	1.25	1.33
IV	Acromegaloid syndrome.....	0.75	0.75	1.00	1.50

TABLE IX  
NON-HYPERFUNCTIONAL HYPOPHYSIAL SYNDROMES

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Hypophysial infantilism.....	0.80	0.80	0.82	0.81
II	Hypophysial tumour.....	1.33	1.50	1.66	1.50

TABLE X  
OTHER ENDOCRINE DISTURBANCES

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Addison's disease.....	0.75	0.80	0.81	1.00
II	Hyperthyroidism.....	0.93	1.25	1.27	1.27
III	Ovarian insufficiency.....	0.95	1.06	1.06	1.11

TABLE XI  
AFFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Epilepsy.....	0.73	0.75	0.76	0.73
II	Epilepsy.....	0.85	0.93	0.85	0.84
III	Post-encephalitic syndrome.....	1.32	1.35	1.70	1.68
IV	Cerebral syphiloma.....	0.72	0.76	0.74	0.72

TABLE XII  
OTHER DISEASES

Case	Diagnosis	Blood Sugar (fasting)	Blood Sugar After Injection of 2 cc. Hypophysial Extract		
			30'	60'	90' After
I	Pellagra.....	0.98	1.02	1.02	1.50
II	Recklinghausens' disease.....	1.14	1.16	1.14	1.14
III	Pulmonary tuberculosis.....	0.85	0.96	0.95	0.95
IV	Pulmonary tuberculosis.....	0.78	0.90	0.86	0.82
V	Tuberculosis spondylitis.....	0.80	0.82	0.86	0.82

Examination of the preceding data shows that in the majority of both normal and sick individuals, the injection of pituitrine produces a slight increase of the blood sugar, which usually attains its maximum about half an hour after the injection, and returns to its original value one hour or sometimes one hour and a half afterwards. In certain cases this decrease reaches below the original figure.

But evidently the intensity of the pituitrinic hyperglycemia varies according to the different pathological conditions. In a certain group, precisely the hyperpituitary patients, this hyperglycemia usually attains figures which are higher than in other abnormal states. Occasionally this post-pituitrinic hyperglycemia does not appear until after the first hour.

If, now, we calculate the average glycemic increase in each of the groups of diseases of the above tables, we obtain the following extremely demonstrative data:

TABLE XIII  
AVERAGE PITUITRINIC HYPERGLYCEMIA IN FOLLOWING DISEASES

I	Hyperpituitarism.....	+37.0 mg.
II	Typical acromegaly.....	+31.8 mg.
III	Other endocrine disturbances.....	+25.0 mg.
IV	Non-functional hypophysial lesions.....	+17.5 mg.
V	Other diseases.....	+16.6 mg.
VI	Diabetes mellitus.....	+14.6 mg.
VII	Lesions of the central nervous system.....	+12.5 mg.
VIII	Diabetes insipidus.....	+11.6 mg.
IX	Normal adults.....	+ 5.9 mg.

It is evident from this table that the pituitrinic hyperglycemia attains more than +30 mgm. in cases of hypophysial hyperfunction, either of the typical acromegalic form, or as more or less openly declared hyperpituitar-

ism. It is exceptional when the hyperglycemia reaches this figure in the other groups of diseases, and always remains much lower in the normal organism.

Individual examination of the cases increases the demonstrative value of these average figures. If we admit +30 mgm. as the characteristic of what we may call the *positive reaction*, it will be seen that this occurred in all except one (observation IX) of the cases of acromegaly (Table VII), and this exception might be explained, perhaps, by the concomitance of a state of intense ovarian insufficiency. In the cases of hyperpituitarism (Table VIII) the reaction was lacking in only one (observation I), which refers to an adult suffering from intense cephalalgia, pronounced development of the skeleton and an evidently extended sella turca.

From Table IX we observe that the reaction was negative in the hypophysial infantilism (observation I), through a pituitary lesion of the hypofunctional type. On the other hand, it was positive in the case of a patient suffering from amaurosis due to a hypophysial tumor, revealed by x-rays (observation II); we suspect, however, that this case, in which the basal metabolism was high, corresponds to others which we have published (22) of hypophysial tumors with latent hyperfunction, which does not give place to the acromegalic symptoms until long afterwards.

In one case of hyperthyroidism (Table X, observation II) the reaction was positive, and seems to indicate the relationship between the hyperglycemic tendency of hyperthyroid and acromegalic patients. We have therefore decided to continue this investigation on our hyperthyroid patients. On the other hand, in all cases of diabetes mellitus (Table V) the reaction was negative and confirms the opinion of those who differentiate between pancreatic hyperglycemia and other glandular hyperglycemias.

The pituitrin hyperglycemia reaction was constantly negative in insipid diabetes (Table VI), in contradiction to Tingle and Imrie (23), who observed an enormous increase of the glycemia half an hour after the injection of pituitrine in a case of this disease, which figure fell to normal shortly afterwards. These authors describe a case of decrease of the post-pituitrin glycemia in diabetes mellitus, and, as we have seen above, this has not been confirmed by our experience.

In a case of post-encephalitic parkinsonism (Table XI, observation III), we obtained a very positive reaction, which may perhaps be explained by the localization of the lesion in the diencephalo-hypophysial system. This hypothesis does not, however, agree with the negative results observed in the diabetes insipidus, in which the lesion is topographically similar, but it may be that the functional type is not the same in one case as in the other.

In a case of pellagra (Table XII, observation I), there was a high but belated hyperglycemia. The latter figure, which we were unable to repeat, induces us to suspect that it might have been due to some technical error.

In a case of Addison's disease (Table X, observation I), we observed a rather accentuated, but belated, reaction: +25 mgm. This does not coincide with the results of certain investigators, as Fritz (11), who suggests that the experimental extirpation of the suprarenal gland prevents the pituitrin hyperglycemia. On the other hand, it confirms Nitzescu's conclusions (24), that the pituitrin hyperglycemia is not fundamentally altered in animals intoxicated with ergotamine, and consequently deprived of excitability of the sympathetic system.

Our results are not authoritative enough to allow us to take part in the discussion now proceeding as to the mechanism of the pituitrin hyperglycemia. We would, however, draw attention to the fact that the scanty effects observed by us in diabetic patients seem to oppose the opinion of many that there is a direct antagonism between the hypophysial incretion and the pancreas incretion. If such antagonism existed, the pituitrine would accentuate the hypoinsulinemia of diabetic patients, and consequently the hyperglycemia and glycosuria. As stated above, our observations coincide with the opinion of those who consider the pituitrin glycosuria as belonging to the group of "extra-insular glycosurias." On the other hand, we are under the impression (through lack of experience we cannot form a conclusive opinion) that insuline is less efficacious in the glycosuria of acromegalic patients than in the case of pancreatic diabetes. Several other authors, amongst them Ulrich, recently (25) are of this same opinion.

Our investigations with Jimena and Moya (26), which coincide with those of Castex and Schteingart (27), show that the hyperglycemic action of pituitrine has no relationship with parallel modifications of the basal metabolism, since the latter, although it increases in some cases after the injection of pituitrine, is not modified in the same cases as the glycemia; in brief, it does not increase specifically in hyperpituitary patients, as does the glycemia.

The most interesting conclusion of our observations is the possibility of applying the examination of the post-pituitrinic glycemia curve to the diagnosis of the hypophysary states, and particularly hyperfunctional states. If the reader will again turn to our tables, it is not necessary to emphasize this point. Parisot (28) proposed the use, for diagnosis of hypophysial diseases, of the alterations of the carbohydrate metabolism after the administration of 300 grams of glucose, followed by the injection of 1 cc. of hypophysial extract. Examination of the glycemia curve, with the patient fasting, as we determine these values, appears to us to be more correct and demonstrative, amongst other reasons, because it eliminates the modifications of the glycemia inherent in taking the glucose, and which may appear under the influence of factors which are independent of the functional tone of the pituitary gland.

## SUMMARY

Examination of the glycemia curve following on the injection of 2 cc. of hypophysial extract when fasting, and determining the blood sugar level each half-hour for an hour and a half after the injection, shows us that both in normal and sick subjects a hyperglycemic state is produced which usually attains its maximum after about half an hour, and returns to its original fasting value after another hour.

This pituitrine hyperglycemia is of an average of 5 mgm. in the normal organism, and attains superior values, which are very variable, in different pathological states.

In explicit or larvate hyperfunctional states of the hypophysis, this hyperglycemia attains higher figures than those observed in other diseases (average 30 mgm).

*Thus an increase of 30 mgm. above the fasting blood sugar level may, in doubtful cases, direct the diagnosis towards hyperpituitarism. But it must be borne in mind that other pathological factors, which modify the usual shape of the glycemia curve, may coincide with the hypophysial alteration.*

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# Book Reviews

THE FUEL OF LIFE. John James Rickard Macleod. Princeton University Press, Princeton, 1928. Pp. 147.

This book summarizes much of the recent experimental evidence regarding the source of the carbohydrate oxidized by muscle tissue, some possible intermediary substances in carbohydrate oxidation, and the rôle of insulin in the process. Macleod believes that fat as well as protein is converted into glycogen before it can be used as fuel for combustion in the muscles and brings together much evidence, both direct and indirect, in support of his view.

HANDBUCH DER BIOLOGISCHEN ARBEITSMETHODEN. E. Abderhalden. Abt. V. Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus. Teil 3 B, Heft 5. Berl. & Wien., 1928. Urban & Schwarzenberg. Pp. 669-822.

This section of Abderhalden's voluminous work on biological methods is of especial interest to Endocrinologists. It is sold separately.

A section on secretion is contributed by Adolph Buckel and Carl von Eweyk. Johannes Hett writes on morphology and experimental studies on the ovary. G. L. Schkawera treats on the methods of investigating isolated organs and J. B. Collip on the preparation and assaying of parathyroid extracts.

The articles are up-to-date and authoritative.

REVUE BELGE DES SCIENCES MEDICALES. Tome I, No. 1. 1929.

This new journal that promises to be of interest and value to Endocrinologists made its initial appearance in January, 1929. It is under the editorial management of Dr. P. Lambin of Louvain. The Editorial Board consists of Professors de Beco, Bessemans, Heymans, Lemaire, Maisin and Rodhain. It is proposed to publish both original articles and abstracts of material appearing in about 25 other Belgian journals.

ESTADO ACTUAL DE LA OPOTERAPIA. E. Bonilla. "La Lectura," Madrid, 1928. Pp. 136.

In this little book Bonilla reviews in an interesting way some of the more significant literature on gland therapy. He traces the development of opotherapy through the Oriental, Greek, Roman and Medieval European periods up to the time of Brown-Séquard. He makes the interesting observation that orchitic substance was recommended as an aphrodisiac in the writings of Suskurutu as early as 600 B.C.

No attempt is made to cover the literature in detail but outstanding articles are considered from the English, French, German and Spanish

literature. The book is of especial interest in that it emphasizes the recent work appearing in Spanish.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, 1928, Bd. III, Lief. V. Curt Kabitzsch, Leipzig. Pp. 204.

Internal secretions and ear, nose and throat. Hans Leicher, pp. 1285-1413.

Internal secretions and blood diseases. H. Hirschfeld, pp. 1414-1440.

Internal secretions and the skin. K. Bingold and E. Delbanco, pp. 1441-1488.

These three articles are useful compilations of the German literature with infrequent references to the work of other nationalities.

THYROIDINE. Edward C. Kendall. The Mayo Foundation, Rochester, Minn. The Chemical Catalog Company, New York, 1929. Pp. 265.

Reviewed in Am. J. Med. Sci. 178: 127. 1929.

SAFE-GUARDED THYROIDECTOMY AND THYROID SURGERY. Charles Conrad Miller. 1928. F. A. Davis Company, Philadelphia. Pp. 261.

This book constitutes a further addition to the now extensive list of manuals on practical goiter surgery.

The author's declared purpose is to emphasize certain phases of diagnosis and treatment that have been neglected or ignored by other writers. The volume is readable and well printed.

DIE ERKRANKUNGEN DER BLUTDRÜSEN. Wilhelm Falta. 1928. J. Springer. Wien and Berlin. Pp. 568.

A somewhat abbreviated version of this book was reviewed in this Journal, 11: 461. 1927. The volume at hand is more satisfactory in that an index is included. So excellent and so well known to endocrinologists is Falta's book that the mere announcement of a second, fully revised, edition will suffice.

FEVER, HEAT REGULATION, CLIMATE, AND THE THYROID-ADRENAL APPARATUS. W. Cramer. 1928. Longmans, Green and Co., London. Pp. 153.

Reviewed in Physiol. Absts. 13: 416. 1928.

PATHOLOGY FOR STUDENTS AND PRACTITIONERS. Edward Kaufmann. 1928. Translated by Stanley P. Reimann, Pathologist and Director of the Research Institute of the Lankenau Hospital. Blakiston, Phila. 3 vol. Pp. 2514.

No endocrinologist, whether he be clinician or investigator, can afford to lack knowledge of the pathology of the organs of internal secretion and the reverberations of distortions of their functions throughout the organism. In the translation of this *vade mecum* of all professional pathologists, Reimann has expanded and enlarged the original with material derived from his own experience, and included new plates, drawings, and photographs from the Lankenau Hospital service, which are a distinct addition. The



treatment of the endocrine glands is almost exhaustive, not only from the point of view of pathological anatomy, but also from the standpoint of the symptomatology which accompanies disorders of these structures. There is no question but that this enlarged edition of Reimann's is the most comprehensive and up-to-date pathology now available in English or any other language. There are many references and the work is thoroughly indexed.

DIE ERKRANKUNGEN DER SCHILDDRUSE. Professor Dr. Burghard Breitner. 1928. J. Springer, Vienna. Pp. 308.

Reviewed in J. A. M. A. 92: 256. 1929.

GREFFE OVARIENNE ET ACTION ENDOCRINE DE L'OVAIRE, ETUDE HISTOLOGIQUE, BIOLOGIQUE, CLINIQUE, ET CHIRURGICAL. Vittorio Pettinaria. 1928. Gaston Doin & Cie, Paris. Pp. 487.

Reviewed in Am. J. M. Sc. 176: 872. 1928.

THE SIMPLE GOITRES. Robert McCarrison. 1928. Wm. Wood & Co., New York. Pp. 106.

The material of this book, originally a Report to the International Conference on Goitre, held under the auspices of the Swiss Goitre Commission at Berne in August, 1927, is very well treated. The book has 143 excellent illustrations. Having devoted more than 25 years to investigation of the simple goitres in India, McCarrison, more than most others, is in position to clarify many phases of this chronically irksome problem in a manner both original and convincing.

Dealing with the parenchymatous or the chronic hypertrophic type of endemic goitre, the following passages illustrate the author's viewpoint: ". . . important as is a sufficiency of iodine in preventing a certain type or types of goitre, it is not a panacea for all types, nor is it proven that its insufficiency is the ultimate cause of any." Again: "Not only is iodine-deficiency held by many to be the sole cause of endemic goitre, but there are some who would seem to attribute exophthalmic goitre to this cause, unmindful of the fact that rare as iodine may be in some regions where endemic goitre prevails, exophthalmic goitre may be rarer still." Also: "It is remarkable how little attention has been paid in literature to Gaylord's important observation regarding the effect of perchloride of mercury, the tendency ever being to extol the influence of iodine, thus restricting the problem of the causation of the disease to too narrow a field." Among his many experiments, McCarrison repeatedly produced goitre in man, employing goitre-producing impure water in volunteers, himself included, and proved that out of 36 subjects 10 developed noticeable goitres. Moreover, the use of intestinal antiseptics in goitre subjects has long been shown by McCarrison to result in the cure of the disease in a goodly percentage of cases.

It is emphasized that the cause of the diffuse colloid type of endemic goitre is to be sought in factors which interrupt the normal cycle of the gland's activity at the stage of colloid storage. To look upon this type of goitre from the narrow point of view of iodine, is comparable to the mechanic who considers the efficacy of his engine solely from the point of view of lubrication. The observation of Hewer to the effect that a correlation exists between the H-ion concentration of the colloid and the secre-

tory activity of the vesicular cells is to be taken into account. McCarrison urges that we look to food deficiencies, food excesses, polluted water supplies, gastro-intestinal affections, and insanitary conditions of life, singly or in combination, as the known goitre-producing causes.

# Abstract Department

On the functional activity of the adrenal gland. Cramer, W., *Am. J. Physiol.* 90: 318. 1929.

Direct evidence of the functional activity of an endocrine organ can be obtained only by a method involving a microscopic technique. In fact, the conception of an internal secretion is at present based only on a theoretical postulate and not on visual demonstration. So many claims of an alleged secretory activity of the adrenal gland have failed to withstand critical examination that a few years ago several workers even raised the question whether the adrenal medulla ever does actively secrete adrenalin into the blood. A simple method has been worked out which renders visible by fixation in osmic acid vapor adrenalin as granules in the medullary cells of the resting adrenal. When the gland is stimulated to activity these adrenalin granules are seen to be expelled into the veins of the gland, giving a clear visual demonstration of "internal secretion." In this way two new facts have been elicited which have an important bearing on the mechanism of heat regulation and on the genesis of fever. 1. Exposure to cold is a powerful stimulus to the adrenal medulla. 2. Prolonged stimulation of the gland leading to a continued adrenalinaemia produces fever. These findings have since been confirmed by Boothby and Sandiford (calorigenic action of adrenalin), Aub, Cannon and their collaborators. The osmic vapor method has confirmed the secretion of adrenalin in asphyxia and in ether anaesthesia, but failed to confirm the alleged secretion of adrenalin in oxygen deficiency and after insulin which has been postulated on the basis of the indirect methods. The method has also rendered it possible to demonstrate a correlation between medulla and cortex and the existence in the adrenal gland of a mechanism which serves to inhibit the functional activity of the gland. It is urged that future investigations on the functional activity of the adrenal should be controlled by this method.—Author's Abst.

Adrenalin in fever. von Euler, U., *Am. J. Physiol.* 90: 340. 1929.

Thunberg's methylene-blue method was used in the way described by Ahlgren. In the evacuated system of minced frog's muscle or rabbit's muscle and methylene-blue, with potassium phosphate as a buffer, the spontaneous oxidation-reduction was studied after addition of serum in various concentrations. Normal human serum shortened the time of decoloration, i.e., activated the oxidation, in concentrations between 1:6 and 1:400. Serum, which was taken from patients with fever or from rabbits after heat-puncture, stimulated the oxidation in the system mentioned above in concentrations as low as 1:6400-1:25,000. The same effect occurred after injection of adrenalin in man or when adrenalin was added to serum directly. This effect in connection with the sensitiveness against alkaline reaction, and the antagonism against insulin and glucose is, as Ahlgren stated, characteristic for adrenalin. The loss of the ability to get fever after adrenalectomy, which is true also for the effect of the heat-puncture (Liljestrand and Frumerie), the reactions of the adrenal glands in long-lasting fevers in connection with the statements made above support the assumption that adrenalin plays a very important rôle in fever.

—Author's Abst.

The hypoglycemic action of allylisopropylbarbituric acid (Numal) is antagonistic to adrenin (Action hypoglycémiante de l'acide Allylisopropylbarbiturique von antagonisme avec l'adrénaline). Fontés, G. and L. Thivolle, *Compt. rend. Soc. de biol.* 99: 1977. 1929.

Numal reduces the hyperglycemia produced by adrenin when the two are injected simultaneously.—J. C. D.

The arterial blood pressure and the blood flow in skeletal muscles in unanesthetized cats as influenced by the intravenous injection of epinephrin. Gruber, C. M., *Am. J. Physiol.* 89: 650. 1929.

Epinephrin in small doses causes a rise in blood pressure during its intravenous injection in unanesthetized cats, but this is followed by a prolonged

fall in blood pressure lasting for several minutes. In some animals only a fall is noted. Epinephrin injected intravenously in small doses in unanesthetized cats causes a dilatation of the vessels of skeletal muscles such as that observed in anesthetized animals, even though no change in blood pressure may be registered on the kymograph surface. No difference was noticed in the effect of larger doses of epinephrin in unanesthetized animals from that commonly observed in anesthetized animals. Epinephrin in large doses causes vasoconstriction of the blood vessels in skeletal muscles, simultaneously with the marked rise in blood pressure. A fall in blood pressure below the normal level is observed following the increase in blood pressure from large doses of epinephrin. Concomitantly with the fall in blood pressure, there is an increase in the blood flow from skeletal muscles.—Author's Summary.

The blood flow in skeletal muscles in unanesthetized cats as influenced by epinephrin. Gruber, C. M., *Am. J. Physiol.* 90: 372. 1929.

Adrenalin chloride 0.1 to 0.5 cc. of a 1:100,000 solution injected intravenously caused either a fall, no change or a rise in blood pressure at the same time it caused an increase in the rate of blood flow from the skeletal muscle. In one animal in which epinephrin caused no increase in blood pressure the rate of blood flow increased from 42 to 72 drops per minute, returning to the control level soon after the injection. Large doses of adrenalin 0.5 to 1 cc. of a 1:10,000 solution caused a rise in blood pressure, in some cases followed by a fall. During the height of increased blood pressure a decrease in rate of blood flow from the muscle was recorded. In most cases preceding and following this decreased flow an increase in blood flow was observed. This increase was recorded even though the blood pressure fell below the control blood pressure level following the rise, e.g., in one cat 1 cc. of a 1:10,000 solution of epinephrin was rapidly injected intravenously and the arterial blood pressure increased from 133 to 250 mm. of mercury with a concomitant decrease in the rate of blood flow from the muscle from 38 to 13 drops per minute. Instead of the blood pressure falling to the normal level, it dropped to 88 mm. of mercury, a fall of 45 mm. of mercury. Four minutes were required for the normal level to be reached and maintained. Simultaneously with the sudden decrease in blood pressure the rate of blood flow from the muscle examined increased to 88 drops per minute or four times the normal rate when the blood pressure was 146 mm. of mercury. From these results we infer that there is no difference in the vaso-motor action of epinephrin on muscle vessels in unanesthetized and anesthetized cats. Since epinephrin produces a dilatation of the blood vessels in one region of the body and at the same time causes vaso-constriction in other regions, the blood pressure recorded must be that of the stronger effect minus the weaker.—Author's Abst.

The carotid sinus isolated and perfused: an area for reflex control of adrenin, output (*Le sinus carotidien isolé et perfusé, zone réflexogène régulatrice de l'adrenalinosecrétion*). Heymans, C., *Compt. rend. Soc. de biol.* 100: 199. 1929.

By the use of three dogs, parabiotically united, it was possible to show that increased pressure in the carotid sinus reduced the adrenin output and that an increase of adrenin followed reduced pressure in the carotid sinus.—J. C. D.

Metabolism and thermo-regulation in decapsulated rats (*Metabolisme et thermo-régulation des rats surrénaloprives*). Houssay, B. A. and A. Artundo, *Compt. rend. Soc. de biol.* 100: 127. 1929.

There is a reduced heat output, shown more strikingly shortly after the operation than later. Resistance to short periods of cold is not strikingly reduced, but prolonged cold is fatal.—J. C. D.

The separation of a new physiologically active principle of the suprarenal gland. Koehler, A. E. and Lillian Eichelberger, *Am. J. Physiol.* 90: 417. 1929.

An epinephrin-free substance has been separated from the suprarenal gland that is capable of elevating the basal metabolic rate and producing improvement in various types of clinical asthenias. The calorigenic activity of this substance administered to animals has proved of great value in its separation

and assay. Its preparation depends upon the separation of epinephrine and other interfering substances such as choline, its activation and finally concentration by the removal of inactive substances. Each of these processes may be accomplished in various ways. Two processes will be described, one depending upon the active principle being carried down with the protein precipitation and the other by its extraction with the lipid fraction. Protein precipitation. The aqueous extract of the fresh glands is adjusted to pH 4-5, preferably 4.8, with acetic or other non-oxidizing acid and the protein precipitated by three-fourths saturation with NaCl or  $(\text{NH}_4)_2\text{SO}_4$ . This precipitate can then be washed free from the uncombined epinephrin. Such a precipitate, or its aqueous or acid extracts, however, have a depressing effect on the basal metabolism and unfavorable clinical actions. If this precipitate is protected from oxygen, the depressing action will disappear on standing and it will acquire the property of raising the metabolic rate. This change can best be accomplished by heating the precipitate with 2 to 3 M HCl on the boiling water bath for ten to fifteen minutes. The active principle can then be separated from the bulk of the protein mass by drying the acid solution in vacuo, so, as to remove all moisture, extracting with absolute methyl alcohol, adjusted to pH 4.5 with ammonia in absolute methyl alcohol (pH measured by transferring small amounts of alcohol mixture to aqueous system) and precipitating with 7 volumes of acetone. Further purification can be effected by redissolving in alcohol and precipitating with acetone. Lipoid extraction. The fresh ground glands are extracted with methyl alcohol-ether mixtures, starting with 80 per cent alcohol and 20 per cent ether and gradually reversing this ratio on subsequent extractions. The alcohol and ether are then distilled off in vacuo and the water-lipoid residue extracted with ether. The separated ether extract is washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the ether evaporated. The residue is then treated with absolute methyl alcohol containing dry HCl gas and heated on the water bath for fifteen minutes. The reaction of the alcohol solution is then adjusted, precipitated with acetone as in the protein precipitation method and similarly purified. Evidence to date indicates that the physiological effect of the substances prepared by these two methods is similar.—Authors' Abst.

**Metabolic studies following the administration of suprarenal extracts.** Koehler, A. E. and A. B. Hastings, *Am. J. Physiol.* **90**: 418. 1929.

It was found that extracts, free from adrenalin, prepared from the suprarenal gland raised the metabolism of dogs and mice when administered orally. The calorogenic effect on human subjects with a low metabolic rate is marked. These subjects exhibit a low mechanical efficiency which is raised to approximately normal by the extract. An attempt has been made to determine what factors are concerned in the alteration in metabolism. The evidence to date indicates that carbohydrates are utilized more efficiently and proteins are spared. A study has also been made of the oxygen consumption  $\text{CO}_2$  production, and lactic acid formation by tissues excised from animals whose metabolism has been altered by various extracts.—Authors' Abst.

**The effect upon the life of rabbits of the removal of the main suprarenals and the accessory suprarenal cortical tissue.** Kojima, T., *Tohoku J. Exper. Med.* **13**: 357. 1929.

In rabbits, the metabolic rate following double suprarenalectomy shows a temporary fall, due to the operation itself, but soon returns to the pre-operative level. In double suprarenalectomized rabbits surviving for over one to two years no alteration in the metabolic rate from the normal was noticed. In these animals accessory cortical tissues were found, especially markedly hypertrophied in the cases surviving a very long time. However, in the cases where the main suprarenals and all the accessory cortical tissues were completely removed or were lacking from birth, the metabolic rate began to fall a few days before death and continued falling during the last days.—Author's Summary.

**Action of tetanus toxin on the adrenal cortex (Action de la toxine tétanique sur la corticosurrénale).** Mouriquand, G., A. Leulier and P. Sedallian, *Compt rend. Soc. de biol.* **90**: 1924. 1928.

In guinea pigs there was no effect of tetanus toxin on the cholesterol content of the adrenal cortex.—J. C. D.

The number of erythrocytes in white rats under different experimental conditions. Nice, L. B., *Am. J. Physiol.* 90: 461. 1929.

Daily injections of one cc. of 1:25,000 adrenalin chloride solution administered subcutaneously into both normal and adrenalectomized white rats caused an augmentation in the number of erythrocytes in the blood drawn from the heart and this increase continued during the course of the experiment, fifty-six days. Emotional excitement produced an increase in erythrocytes in the blood of normal rats, but no change in the count of adrenalectomized or splenectomized rats. This augmentation in erythrocytes seems to come from the reservoir in the spleen.—Author's Abst.

The influence of the adrenals on the urea-forming and barrier function of the liver (*Ueber den Einfluss der Nebennieren auf die harnstoffbildende und Barrierefunktion der Leber*). Putschkow, N. W. and W. W. Krassnow, *Arch. f. d. ges. Physiol.* 220: 44. 1928.

After adrenalectomy (dogs and cats) there is a definite increase in the amino-acid and biogenous nitrogen in blood and urine and a concurrent sharp decrease in urinary urea; such changes are identical with those following cessation of liver function or experimental removal of the liver. The biogenous amines are especially affected, and to this is to be attributed those fatal terminations in which accumulation of choline is undoubted. The isolated liver of adrenalectomized animals disposes of ammonium salts and biogenous amines more feebly than does the normal liver, and its urea output is lowered. Extract of fresh adrenals restores the barrier and urea functions of the liver. The active principle in such an extract is extraordinarily labile and is decomposed in 15 to 20 minutes. It is not adrenine and is not present in other organs.

—A. T. C.

Tetany following the use of cocaine and epinephrine in intranasal operations. Roberts, S. E., *J. A. M. A.*, 93: 905. 1929.

Tetany is a frequently overlooked symptom complex following the use of cocaine and epinephrine in the nose. No direct references in the literature could be found. It is not a serious complication, but a very distressing one for the patient if untreated. It is not a drug intoxication. It is not due to a condition or a single drug, but to a combination of hypoparathyroidism, hyperventilation and epinephrine in nervous, emotional patients. It is satisfactorily and quickly relieved by subcutaneous administration of parathyroid extract. (Collip).—Author's Summary.

Functions of the adrenal glands. Rogoff, J. M. and G. N. Stewart, *Am. J. Physiol.* 90: 497. 1929.

It has been well established that the function of the epinephrine secretion from the adrenals is not indispensable. The important function of the glands consists of the elaboration and probably secretion of a hormone by the cortex. To distinguish this hormone from adrenalin and to indicate its origin in the interrenal tissues, we have employed the name, "Interrenalin." Marked prolongation of life has been observed by us in adrenalectomized animals when extracts of adrenal cortex were administered. Beneficial influence has been obtained, in a number of cases of Addison's disease, by administration of these cortical extracts.—Authors' Abst.

A quantitative study of human adrenals. 1. Is it possible to have a hyperfunction of adrenal tissue comparable to the hyperfunction known to exist in the thyroid gland? Schultz, W. H., *Am. J. Physiol.* 90: 508. 1929.

Improved methods for assaying biologically and colorimetrically were used in studying quantitatively fresh human adrenal glands. An extensive study was made of a tumor of the adrenal gland removed from a patient diagnosed as "accessory adrenal" by virtue of the periodic hypertension amounting to as much as 260 mm. blood pressure. Extracts of this tumor compared with other fresh adrenal extracts revealed an unusually rich adrenalin content.

—Author's Abst.

**Clinical experience with Addison's disease.** Snell, A. M. and L. G. Rowntree, *Ann. Int. Med.* 3: 6. 1929.

From the records of the Mayo Clinic about 300 definite or tentative diagnoses of Addison's disease have been made. Of these cases, 103 have been found to be authentic examples. Syphilis was present in only four patients. Of the 30 cases autopsied, 26 had tuberculosis and in four there was simple atrophy of the adrenals. The cardinal symptom, asthenia, was present in every case. Enfeebled circulation and nervous symptoms were also prominent. Pain in the back has also been a persistent symptom. Gastro-intestinal disturbances varying from mild anorexia and nausea to violent vomiting have been present in every case. Diarrhea has usually been a terminal symptom. The pigmentation is increased, due to pressure from clothing. Urinalysis usually shows that there is renal involvement. Anemia, contrary to Addison's opinion, is rare, and when it is present it is usually due to some complication. Tuberculosis was demonstrated in other parts of the body in one-third of the cases. The authors found that the triad: hypotension, hyperpigmentation and asthenia, was very suggestive of suprarenal disease. The terminal picture in Addison's disease suggests intoxication. The Muirhead treatment (epinephrine, hypodermically and rectally, and adrenal cortex by mouth) has caused temporary improvement in some cases. The pigmentation fades and the gastro-intestinal symptoms subside. The terminal symptoms did not respond to any treatment which was used. The authors believe that the patient should be protected from all tiring influences.—E. L.

**On the chemistry of the adrenal cortex.** Szent-Györgyi, Am. J. Physiol. 90: 536. 1929.

The adrenal cortex contains a highly reducing substance, which is specific for the interrenal system and has been isolated as crystals. It is a hitherto unknown isomer of glycuronic acid. The substance is capable of acting as a powerful catalyst of certain biological oxidations and under certain conditions inhibits pigment formation in minute quantities (1:0,000,025 per cent). An identical substance has been isolated from peroxidase-plants. Here the substance is clearly connected as catalyst with the peroxidase system. Some chemical properties of the substance are demonstrated.—Author's Abst.

**Studies on suprarenal insufficiency. IV. The blood sugar in suprarenalectomized rats.** Wyman, L. C. and B. S. Walker, *Am. J. Physiol.* 84: 215. 1929.

The normal blood sugar range in the rat, by the Folin micro-method is found to be from 61 to 110 mgm. per cc. whole blood, with an average value of 82 mgm. Following double suprarenalectomy, coincident with the appearance of marked symptoms of subacute insufficiency, the blood sugar values fall to between 50 and 60 mgm. In the terminal convulsive stages they may be as low as 30 mgm. In rats with chronic suprarenal insufficiency, but showing no marked symptoms, the blood sugar may fall to the lowest portion of the range of normal values and be maintained at that level, occasionally dropping below the normal low limit. In rats possessing either gross accessory cortical tissue or successful cortical transplants, in the absence of demonstrable chromaffin tissue, the blood sugar remains within the normal range. The blood sugar is normal following control blank operation, showing that the results observed after suprarenalectomy are not produced by operative trauma. The results indicate that the low blood sugar observed after suprarenalectomy is associated with cortical insufficiency. It is suggested that the cortex is concerned in the steady maintenance of a normal blood sugar level, while the medulla is an important adjunct for rapid adjustment under emergency conditions.—Authors' Summary.

**Cortical and medullary factors in suprarenal insufficiency.** Wyman, L. C., *Am. J. Physiol.* 90: 563. 1929.

A series of studies on suprarenal insufficiency in the albino rat has been approached by using normal rats, blank operated control rats, suprarenalectomized rats having autoplasmic cortical transplants but no demonstrable chromaffin tissue, and suprarenalectomized rats which exemplified all phases of suprarenal insufficiency from acute and subacute to chronic. The results have

led to the following conclusions. Increased susceptibility to histamine poisoning and to anaphylactic shock in suprarenalectomized rats is not related to cortical insufficiency, but is consequent to the lack of medullary tissue. Low blood sugar is characteristic of suprarenal insufficiency in rats and is associated with cortical insufficiency. Following double suprarenalectomy in rats the non-protein and urea nitrogen may be increased, the amount of increase tending to parallel the severity of the symptoms of cortical insufficiency. In suprarenalectomized rats the fall of body temperature upon exposure to moderate cold and the inability to recover normal temperature rapidly is correlated with the degree of cortical insufficiency which is present. On the basis of the results of these studies and those of other investigators, it is suggested that the suprarenal cortex is concerned in the steady maintenance of certain bodily conditions, while the medulla brings about rapid adjustments in the same direction under emergency conditions.—Author's Abst.

**Vagal tonus, a function of circulating adrenin (Le tonus vagal, fonction de l'adrénalinémie).** Viale, G., *Compt. rend. Soc. de biol.* 90: 2008. 1929.

Section of the vagus after the injection of ergotamine in dogs does not cause a cardiac acceleration. Ergotamine injected after cutting the vagus slows the heart, but increases the amplitude of the beat. Exclusion of adrenin from the circulation, by removal of one adrenal and ligation of the vein from the other, prevents the acceleration after the vagus is cut. These experiments support the author's view that circulating adrenin acts on the sympathetic endings in the heart and the vagal centers in the medulla, thereby maintaining the normal heart rhythm.—J. C. D.

**Normal values of basal or standard metabolism. A modification of the duBois standards.** Boothby, W. M. and Irene Sandiford, *Am. J. Physiol.* 90: 290. 1929.

Basal or standard metabolic rates have been made in our laboratory on more than 60,000 individuals, up to December, 1926. From this number we have selected 6,888 subjects (1,822 males, 5,066 females) who on careful physical examination revealed no abnormalities which would influence their rate of heat production. Included in this series are the 262 school children to be reported by Sandiford and Harrington. The data are expressed on the basis of calories per square meter referred to age for both males and females, using the height-weight formula of duBois and duBois for the following reasons: 1. duBois was the first to develop a practical clinical standard of heat production. 2. The statistical treatment of our series supports the accuracy of the original duBois standards, being only 1 to 4 per cent lower for the adults and 3 to 7 per cent lower for children down to the age of fourteen. 3. The utilization of the height-weight factors combined to represent surface area and the adoption of standards on the basis of age for each sex has the great advantage of indicating simply and clearly the difference in the rate of the basal metabolism between men and women. 4. This method of expression likewise clearly shows the rapid decrease in rate of the basal metabolism of male children between the ages of five and twenty-one and the more rapid decrease in female children between the ages of five and seventeen, followed in both sexes by a gradual and nearly parallel decline to old age. 5. Finally, it permits of the correlation of the rapidly decreasing heat production from infancy to maturity and the more slowly decreasing heat production of adult life on the basis of the phenomena of intracellular motion, inevitably accompanied by increased heat formation, associated with the act of mitotic cell division.—Authors' Abst.

**The influence of endocrine glands on the amount of water in striated muscle (Action des glandes endocrines sur la teneur en eau des muscles striés).** Parhon, C. J., M. Kahane and V. Marza, *Compt. rend. Soc. de biol.* 100: 40. 1929.

Sheep, cats and dogs, but mostly guinea pigs, were used. Thyroidectomy markedly raised the water content. A less constant and less marked rise followed spaying, castration, thymectomy, thyroparathyroidectomy, over-feeding with thymus, pregnancy, and injection with placental or cerebral lipoids. The water content was reduced by treatment after thyroidectomy, also after injection of adrenin, insulin, posterior lobe extract, and of lipoids derived from the adrenals, or the ovaries.—J. C. D.



**On the regulation of the normal water-intake in rats and its experimental modification through brain punctures (Experimental diabetes insipidus).** Richter, C. P. and M. E. Brailey, *Am. J. Physiol.* **90**: 494. 1929.

Daily water-intake was measured in 52 rats. It increased gradually with age, and was greater for the males than for the females. The gradual increase in water-intake with growth in the female as well as in the male suggested its relationship to body-weight. But body-weight was found to increase very much more rapidly than water-intake. There was, however, a perfect correlation with body-surface. At ages from 30 to 160 days all rats of either sex drank about 800 cc. per square meter body-surface per day. Various attempts have been made to modify water-intake, but only results produced by punctures made in the brain stem are reported. Lesions were made through the base of the brain with a fine scalpel in the region of the sella tūrcica. In 13 out of 40 animals increase in water-intake was produced. In one animal the water-intake increased from 25 cc. to 260 cc. per day, the maximum intake representing twice the animal's own body-weight. In others the increase was not so marked. The diabetic state seemed permanent, for at the time the animals were killed the water-intake was still as high as at the beginning six months before.

Authors' Abst.

**Comparative influence of insulin and thyroxin on the endocrine glands (Action comparée de l'insuline et de la thyroxine sur les glandes endocrines).** Watrin, J. and P. Florentin, *Compt. rend. Soc. de biol.* **100**: 111. 1929.

Injectons of insulin cause, in guinea pigs, hyperplastic activity in the thyroid and hypophysis. Thyroxin produces loss of weight with degenerative changes, particularly in the pancreatic acinar tissue. There is an increase in the number of islands.—J. C. D.

**The endocrine conditions essential for the production of deciduomas (Conditions endocriniennes de la formation de déciduomes).** Brouha, L. and H. Simonnet, *Compt. rend. Soc. de biol.* **99**: 1926. 1928.

In rats the life of the corpus luteum can be prolonged by extracts of the anterior lobe of the hypophysis. Using this method and that of producing oestrous when desired by doses of folliculine, the authors found that typical deciduomas were produced only when the action of folliculine was followed by that of corpus luteum. Implantation of the egg they conclude depends on the consecutive action of these two hormones, not on the action of corpus luteum alone.—J. C. D.

**The masculinization of capons with bull serum from the point of view of the law of special thresholds and the "all or none" law (La masculinisation des chapons par le sérum de toureau considérée a point de vue de la loi des seuils différentiels et de la loi du "tout ou rien").** Busquet, H., *Compt. rend. Soc. de biol.* **99**: 1855. 1928.

As in partial castration there are dosages at which the different sex characters appear. The order in which they appear with increasing dosage is not the same as that found with increasing masses of testis, crowing being the first in the former and the reddening of the comb in the latter. Within narrow limits, the law of special thresholds for each character holds in both types of masculinization. If the sex hormone available is in excess or below these narrow limits the "all or none" law holds.—J. C. D.

**Folliculin from urine of pregnant women.** Doisy, E. A., C. D. Veler and S. Thayer, *Am. J. Physiol.* **90**: 329. 1929.

A study of the extraction of folliculin from urine has shown that chloroform and olive oil are the best solvents of those tested. Using chloroform and a continuous liquid extraction apparatus, large quantities of the crude extract have been prepared. The apparatus used permits the extraction of about 30 liters of urine per 24 hours with a recovery of over 75 per cent of the hormone. The crude extract is refined according to the principles outlined below. The extraction with olive oil has proved to be quite satisfactory, about 50 per cent of

the folliculin being removed by stirring the urine for half a hour with an amount of olive oil equal to 1/20 of the volume of urine. The hormone is then transferred to ethyl alcohol, the concentration of alcohol reduced to 70 per cent with water, and the alcoholic solution extracted with petroleum ether. The alcoholic solution is distilled, the residue dissolved in butyl alcohol, and this alcoholic solution extracted with dilute sodium hydroxide. The butyl alcohol is distilled, the residue leached with ethyl ether, the ether distilled and the residue dissolved in butyl alcohol. Petroleum ether is added and the precipitate discarded. The hormone is then extracted from the butyl alcohol-petroleum ether solution with dilute acids or alkalis. Separation of the hormone from the aqueous solution and a repetition of the aqueous extraction has given a product of which 1 rat unit weighs less than 0.001 mgm. An attempt to apply the procedure described for the preparation of aqueous solutions from liquor folliculi to urines, resulted in failure. This failure of the liquor folliculi method might have been due to either (a) a difference in the contaminating substances, or (b) a chemical difference between the physiologically active substances of liquor folliculi and urine. In line with the latter possibility is the paradoxical situation of the large amount of folliculin in the blood and urine during pregnancy, yet the reports of abortion produced by injections of the oestrous hormone. Working with the highly purified preparations (1000 R. U. per mgm.), we can say that the solubilities give no reason for doubting the identity of the two products. In addition, a certain set of reactions of the hormone from the two sources with benzoyl chloride and  $\alpha$ -naphthyl isocyanate yields the same results. Since our evidence, both chemical and physiological, points to the identity of the active material of the liquor folliculi and urine, and the simple procedure of preparation described yields a very pure product from a readily available, cheap source, clinical and experimental work with the oestrous hormone will be greatly expedited.

**Irradiation of ovaries and hypophysis in menstrual disorders.** Ford, F. A. and D. G. Drips, *Radiology*, 12: 393. 1929. Abst., *Arch. Physical Therapy*, 10: 426.

Irradiation of ovaries or hypophysis has been effective in re-establishing menstruation in patients in whom prolonged use of organotherapy had been ineffective. A conclusion cannot be drawn as to the comparative efficiency of methods because the cases selected for irradiation were of unusual severity. Irradiation of the hypophysis, occasionally combined with splenic and hepatic irradiation, has exerted a temporary regulating effect in 7 cases of severe menorrhagia and metrorrhagia; with supplementary treatment, the effect in two cases has persisted more than one year. Relief of dysmenorrhea has been incidental in certain cases of menorrhagia and oligomenorrhea. Of 6 cases treated primarily for dysmenorrhea, relief has been complete in three and has lasted for a period of four to six months; improvement occurred in two others. Irradiation of ovaries of white rats in various dosages has resulted as follows: There was no continued influence on the regularity of the estrual cycle. Complete destruction of follicles did not result from dosage up to 2.5 unit skin doses.

**The sex hormones.** Funk, C., *Am. J. Physiol.* 90: 353. 1929.

The male and female sex hormones show far reaching analogies in their chemical behavior. Both substances can be extracted from various sources by means of chloroform and are soluble in dilute alkalis. If one subjects crude extracts to the action of alkalis, the active substances are found in the non-saponifiable fraction. We are dealing here either with fatty acids, or, which is more likely, with phenols or alcohols. The lessened activity of the sex hormones in the form of their aqueous solutions suggests a separation into two constituents, one of which is less soluble than the other.—Author's Abst.

**Notes on the antagonism between the follicle and the corpus luteum (Quelques considérations sur l'antagonisme entre le follicule et le corpus jaune).** Goormaghtigh, N. and A. Amerlinck, *Compt. rend. Soc. de biol.* 100: 439. 1929.

Normal mice injected regularly with folliculine showed prolonged oestrous periods. The corpora lutea developed slowly and to only a slight degree. This is further proof of antagonism between folliculine and the corpus luteum.  
—J. C. D.

**Recent studies on transplantation of desiccated ovaries** (*Nouvelles observations sur la transplantation d'ovaries après dessiccation*). Kallas, H., *Compt. rend. Soc. de biol.* 100: 97. 1929.

In guinea pigs, the vitality of ovaries for grafts is much reduced when they have lost more than 40 per cent of their weight through drying, and entirely destroyed at 60 per cent.—J. C. D.

**On the cyclic vaginal changes in spayed animals** (*Sur un rythme vaginal chez les animaux ovariectomisés*). Kostitch, A. and A. Télébakovitch, *Compt. rend. Soc. de biol.* 100: 51. 1929.

In spayed white mice the vaginal smears show cyclic changes similar to but less intense than those of normal oestrous. These are associated with changes in the cells of the vaginal epithelium, which do not, however, show the stage of keratinization characteristic of normal oestrous. Cyclic vaginal changes then are not dependent on the corpus luteum or the ovary.—J. C. D.

**Results of oral administration of female sexual hormone "Menformon"** (*Über weibliches (sexual) hormon Menformon. Weitere Erfahrungen über Wirkung oraler Gaben*). Laqueur, E. and S. E. de Jongh, *Klin. Wchnschr.* 7: 1851. 1928. *Abst., Physiol. Absts.* 14: 52.

To produce oestrus in rats by oral administration of "menformon" 100 times the subcutaneous dose is required. In mice 11 times the subcutaneous dose is effective when given orally. When given by the rectum, rats require 25 times the subcutaneous dose to produce oestrus. In rats, 900 mouse units produced marked growth of the uterus within 11 days. In male rats the hormone in a period of 6½ weeks retarded the growth of the genitalia. In male guinea-pigs, oral administration of the hormone caused the mammary glands to grow considerably, and in one instance they produced milk.

**Transplantation of ovaries after drying** (*Transplantation d'ovaries après dessiccation*). Lipschütz, A., *Comp. rend. Soc. de biol.* 100: 95. 1929.

In guinea pigs desiccated ovaries can be grafted provided the drying is not too great.—J. C. D.

**Transplantation of preserved ovaries. I. Endocrine action of ovaries preserved on ice** (*Transplantation von konservierten Ovarium. I. Endokrine Wirkung von auf Eis konservierten Ovarien*). Lipschütz, A., *Arch. f. d. ges. Physiol.* 220: 11. 1928.

Ovaries kept at temperatures below 0° C. are damaged to such an extent that following transplantation only degeneration occurs. Ovaries kept at +1 to +3° for from 1 to 16 days and then transplanted (guinea-pigs) retain activity and are capable of hyperfeminizing male animals, the effect lasting for 5 months or more. Six positive results have been obtained with ovaries preserved for from 1 to 3 days, and five positive results with ovaries preserved for 7 to 16 days. Some damage results from the preservation; the proportion of successful results is less than with freshly transplanted ovaries, the latent period of action is lengthened, and the survival period is shorter.—A. T. C.

**The ovarian hormone in relation to women.** McClendon, J. F., C. Conklin, F. Wildebush and H. Wiles, *Am. J. Physiol.* 90: 448. 1929.

From biometric analysis of 438 determinations of basal metabolism on ten women, including the calculation of the probable errors, it was shown that the basal metabolism rises during the pre-menstrual period and falls during menstruation to the lowest level during the post-menstrual period. The excretion of the ovarian hormone follows the same curve. During menstruation no ovarian hormone could be determined in the urine. During the post-menstrual period four single-injection mouse units were recovered from a 24-hour specimen of urine. During the pre-menstrual period 20 single-injection mouse units were recovered from a 24-hour specimen of urine. The hormone seemed to be present in the blood plasma during the greater part at least of the inter-menstrual

period. None was found in the corpuscles. Owing to the positive correlation between the hormone and the basal metabolism an attempt was made to raise the basal metabolism by injecting the hormone. It was found that the single-injection doses up to about 4,000 mouse units at 8:00 a. m. was followed by a very slight rise in the metabolism to 6:00 p. m., but owing to the necessity of withholding food, the metabolisms were interrupted. At 8:00 a. m., the next day there was a normal basal metabolism. The metabolism of the same subjects without injection of hormone rose slightly during the day, but not as much as with injection. By giving several injections a day it was possible to raise the metabolism still higher and also cause an increase in metabolism the following day. Women who had never menstruated showed none of the hormone in their blood. Injections of hormone were made into women who had never menstruated and who were undeveloped in secondary sexual characters and accurate measurements of the secondary sexual characters were made. In women who had menstruated but at the time had had amenorrhea of considerable duration, injection of the hormone caused menstruation to occur again.—Authors' Abst.

**Thyroid tissue tumors of the ovary (with the report of an apparently toxic case).** Moench, G. L., Surg. Gynec. Obst. 49: 150. 1929.

Three cases are reported, one of which seems to have contained actually functioning thyroid tissue. Hence Bauer's assumption that cases of struma ovarii are really pseudomucinous ovarian cysts or cystadenomata ovarii is denied, and they are considered to be teratomata.—A. T. C.

**The effect of bilateral ovariectomy in cats upon sensitivity to insulin.** Myers, W. K., Am. J. Physiol. 89: 610. 1929.

Bilateral ovariectomy in cats caused an immediate increase in sensitivity to insulin. There was a gradual recovery of resistance to insulin to such an extent that the sensitivity was subsequently diminished in comparison with that of the intact animal. Blood sugar levels and the general reaction to insulin did not coincide from time to time. This would suggest that insulin shock and hypoglycemia are separate and distinct manifestations resulting from the injection of insulin. There seems to be an exaggeration of their independence following the recovery of the animal from the immediate effects of ovariectomy. Bilateral ovariectomy was followed in these cats by a marked and unmistakable increase in weight.—Author's Summary.

**Note on changes in testicular grafts in the goats and rams (De l'évolution des greffes testiculaires du Bouc et du Bélier).** Retterer, E., Compt. rend. Soc. de biol. 100: 168. 1929.

The grafts described were one and two years old and showed the steps in the gradual alteration and disappearance of the parenchymal cells and their replacement by connective tissue.—J. C. D.

**Amblyopia recidive after operative removal of the ovaries.** Rosenstein, A., Ztschr. f. d. ges. Neurol. u. Psychiat. 115: 13. 1929. Abst., Arch. Neurol. & Psychiat. 21: 1186.

In spite of the great frequency of female genital disorders, periodic blindness has not been reported up to the present time. Rosenstein reports a case of a woman, aged 29, who in 1926 first noted migrainous attacks with dimness of vision which occurred very irregularly. About three months later she had a total extirpation of the uterus, leaving an ovarian rest. One month after this she had blindness, lasting from three to four days, with her migrainous attacks, and thereafter she had this periodic migraine and blindness every four weeks at the time of her menses. The visual disturbances began and ended with concentric shrinking of the visual field, and with loss of color vision, only the green remaining intact. The pupils became wide, while the fundi did not show any changes in either the vessels or the nerve heads. The convergence reaction of the pupils was decreased, accommodation was not interfered with, and the external ocular muscles were not involved in the attacks. Examination of the rest of the nervous system gave negative results, and the spinal fluid was

entirely normal. Following ovarian therapy, the condition improved. The author attributes the transient blindness to a nerve rather than a retinal disturbance, and says that concentric narrowing of the visual field as seen in this case is characteristic of many diseases of the optic nerve, as, for example, in optic atrophy.

**Body changes following experimental castration (Modifications morphologiques après castration expérimentale).** Werner, G., *Compt. rend. Soc. de biol.* 100: 47. 1929.

Young sheep and guinea pigs when castrated gain weight less rapidly than controls, while the reverse is true in adults. Castrates lose weight less rapidly in starvation. There are also body changes in the sheep after castration which involve the head and teeth.—J. C. D.

**Studies on the modifications of the sugar, calcium, and urea in the blood following experimental castration (Recherches sur les modifications de la glycémie, de la calcémie et de l'urémie après castration expérimentale).** Werner, G., *Compt. rend. Soc. de biol.* 100: 49. 1929.

Rabbits, guinea pigs, sheep and dogs were used. There was an increase in these animals of all three substances after castration.—J. C. D.

**Action of the anterior lobe extract of the hypophysis on the basal metabolism in man (Action de l'extrait du lobe antérieur de l'hypophyse sur le métabolisme basal chez l'homme).** Castex, M. R. and M. Schteingart, *Compt. rend. Soc. de biol.* 100: 121. 1929.

Subcutaneous and intramuscular injections in man of commercial extracts of the anterior lobe raised the basal metabolic rate in eighteen cases and reduced it in seven.—J. C. D.

**Secretion into the blood stream from the anterior lobe of the hypophysis in the cat (L'excrétion hémocrine dans le lobe antérieur de la glande pituitaire chez le chat).** Collin, R., *Compt. rend. Soc. de biol.* 100: 107. 1929.

The "black granules" seen in the sinusoids of the pituitary may be broken down red blood cells, since a drop of anterior lobe substance, obtained from fresh crushed gland, haemolyzes blood.—J. C. D.

**Concerning the hypophyseal (Pars Distalis) hormones for growth and for reproductive processes.** Cushing, H. and H. M. Teel, *Am. J. Physiol.* 90: 323. 1929.

Experiments in this laboratory with the injection of anterior lobe extracts on dogs confirm the recent work on rats and mice (Evans, Smith) in establishing the fact that there are two distinct hormones. 1. The growth principle. Intraperitoneal injections in dogs cause in time a pathological overgrowth with splanchnomegaly, hyperplasia of thyroid and adrenal cortex in association with the following symptoms: polyphagia, polydipsia, polyuria, sialorrhea, lactation, asthenia and physical inactivity. In the females the genitalia become enlarged in the absence of oestrus; in males, testicular atrophy occurs and libido is diminished. Chemically: no elevation of the basal metabolic rate has been demonstrated; blood cholesterol tends to be elevated; no observable change occurs in serum protein, in calcium, phosphorus or sugar. It has been shown, however, that the non-protein nitrogen in the fasting blood falls approximately 25 per cent following injection of the growth principle. 2. The sex principle. Boiled dilute acetic acid extracts of very fresh bovine glands (anterior lobe), made according to the method described by Spaul (1924) for producing premature metamorphosis in salamanders, have brought about premature oestrus in twenty-six day old female rats. The ovaries enlarge though to a less extent than the enlargement produced by Smith's method of introducing living anterior lobe transplants. Not all extracts produced by this method have proved to be active, but the results make it evident that the sex principle may sometimes be present in acid extracts which invariably destroy the growth principle.

—Authors' Abst.

A comparison of anterior hypophyseal implants from normal and gonadectomized animals with reference to their capacity to stimulate the immature ovary. Evans, H. M. and Miriam E. Simpson, *Am. J. Physiol.* 89: 371. 1929.

The authors determined that castration and, to a less extent, cryptorchidism, result in increase in the size of the hypophyses and in an augmentation of their ability to promote sexual development when used as transplants.

—R. G. H.

A comparison of the ovarian changes produced in immature animals by implants of hypophyseal tissue and hormone from the urine of pregnant women. Evans, H. M. and Miriam E. Simpson, *Am. J. Physiol.* 89: 381. 1929.

With certain limits, the weights of ovaries stimulated to precocious development by implants of rat anterior hypophyseal tissue are roughly proportional to the amount of tissue implanted. If four times the minimal dose is given, the ovaries are increased approximately four times in weight. On the other hand, if four times the minimal extract dose be given, the resulting ovaries are not appreciably heavier. The minimum dose of extracts of the urine of pregnant women can be increased one hundred and sixty fold and the resulting ovarian tissue in the young female is barely trebled thereby. This difference in the weights of ovaries that develop as a result of implant and of extract treatment is primarily due to difference in the number of follicles stimulated. The minimal effective implant treatment stimulates a much more general follicular development than does the corresponding dose of urine extracts, where a small number on "crop" of follicles are picked out by the hormone and carried to the corpora lutea stage.—Authors' Summary.

Comparative physiology of the anterior lobe of the hypophysis (*Physiologie comparée du lobe antérieur de l'hypophyse*). Lipschütz, A., H. Kallas and E. Wilckens, *Compt. rend. Soc. de biol.* 100: 28. 1929.

Uterine changes are produced in young mice by injection of large amounts of anterior lobe from the pigeon. This shows that the pigeon gland also contains oestrous producing substance, though to a smaller degree than the pituitaries of mammals.—J. C. D.

New experiments on the pituitary hormone and the law of puberty (*Nouvelles observations sur les hormones hypophysaires et la loi de la puberté*). Lipschütz, A. and H. Kallas, *Compt. rend. Soc. de biol.* 100: 30. 1929.

Extracts from the hypophysis of very young guinea pigs and from a senile dog, when injected into mice, produced a characteristic, though weak, stimulation of oestrous.—J. C. D.

The pituitary gland and the suprarenal cortex. Moehlig, R. C., *Arch. Int. Med.* 44: 339. 1929.

From a review of the literature it is concluded that anencephalus is accompanied by pituitary anomalies. The degree of anomaly varies in different cases, being greatest in anterior cerebral defects. The suprarenal cortex reflects the state of the pituitary gland and is always hypoplastic when the pituitary is involved in anencephalus. Hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex. The view that cerebral defects are responsible for aplasia of the suprarenal cortex must be modified to the view that the pituitary gland is the responsible factor. It is to be emphasized that only the suprarenal cortex and not the medulla is involved in these pituitary anomalies, and the same holds true for experimental hypophysectomy. The embryohormonic relation of the pituitary to mesenchymal tissues gives a clearcut explanation of this singular involvement. The importance of the relation of the pituitary gland to the suprarenal cortex is readily realized when cholesterol metabolism is considered. Many related problems can be studied with a newer and better foundation.—Author's Summary.

**Primary pituitary tumors.** Puestow, C. B., Arch. Neurol. & Psychiat. 22: 547. 1929.

In a series of 50 primary tumors of the pituitary body more than 60 per cent were adenomas. Malignant lesions were found in 16 per cent of cases. Growth stimulation, manifested chiefly by acromegaly, was not found in cases other than in those of adenoma. Amenorrhea was present in 13 of 14 cases of adenoma and in only two of six cases of malignant lesions.

—Author's Summary.

**Studies in acromegaly. VIII. Experimental canine acromegaly produced by injection of anterior lobe pituitary extract.** Putnam, T. J., E. B. Benedict and H. M. Teel, Arch. Surg. 18: 1708. 1929. Abst., Physiol. Absts. 14: 244.

This paper records the first successful attempt to produce acromegaly experimentally in higher animals. The experiment was conducted with two pedigree, thoroughbred English bulldogs, female litter mates, aged 4 weeks. During the 3 weeks that they were kept under observation before the experiment began, they increased in weight normally and equally. On April 7, 1927, they weighed, respectively, 4.87 and 5 kgm. The lighter animal was then injected with 10 cc. of specially prepared anterior lobe extract, this being continued daily during the course of the next 14 months with gradually increasing doses, the animal receiving 75 cc. just before her death. The control animal received daily corresponding amounts of sterile saline. Within a month it was evident that the dog which received the anterior lobe substance was growing considerably faster than the control, and from then on the rate of growth was so much more rapid that she eventually acquired twice the weight of the control (45 kgm. as opposed to 23 kgm.). In addition, the animal showed enlargement of the tongue, great increase in the size of its bones, prognathism, pendulous skin, enormous hypertrophy of the mammary glands, with the production of colostrum and marked hypertrophy of the sexual organs. The animal eventually succumbed after exposure to the sun for some hours on a hot day. The control was then sacrificed and complete necropsy of both animals was carried out with microscopic study of all tissues and glands. The chief features of the necropsy were the marked signs of skeletal overgrowth with hyperostosis, generalized splanchnomegaly affecting particularly the thyroid and genital tract, adenomas of the suprarenal, and many ripe but unruptured follicles in the ovaries. The tissues of the control were entirely normal, grossly and microscopically. The observation is regarded as due to the effect of the two anterior lobe hormones of the growth-promoting and the sexual principles.

**Is pituitary secretion concerned in the inheritance of body-size?** Robb, R. C., Proc. Nat. Acad. Sc. 14: 394. 1928. Abst., Arch. Neurol. & Psychiat. 21: 1202.

A comparison was made of the weights of the pituitary bodies in giant (Flemish) and dwarf (Polish) male rabbits and in their  $F_1$  hybrids. There is no characteristic difference in the weight of the pituitary body that may be correlated with the differences observed in growth rate. With increase in body weight, a progressive decrease in relative pituitary weight occurs. In the full-grown dwarf rabbit, accordingly, there is relatively twice the amount of pituitary substance observed in the adult Flemish giant rabbit.

**The action of anterior lobe of the hypophysis on milk secretion (Action du lobe antérieur de l'hypophyse sur la montée laiteuse).** Stricker, P. and F. Grueter, Compt. rend. Soc. de biol. 99: 1978. 1929.

In rabbits, injections of anterior lobe extract produces lactation only after the mammary gland has been acted on by corpus luteum. In dogs and rabbits it will re-establish milk flow up to two weeks after weaning.—J. C. D.

**The effect of extracts containing the growth principle of the anterior hypophysis upon the blood chemistry of dogs.** Teel, H. M. and O. Watkins, Am. J. Physiol. 89: 662. 1929.

The blood of fasting dogs was analyzed just before and for a number of hours after the injection of growth promoting extracts of the anterior hypophysis of the ox. During the experimental period no significant changes were found

in total phosphorus preformed or total creatinine, uric acid or sugar. A drop in serum calcium following the injection was often but not always observed. Very slight changes in inorganic phosphorus sometimes occurred, but the findings were not consistent. A marked drop in non-protein nitrogen, however, was always observed after the injection of an active extract (20 to 30 per cent). The disappearance of some urea and amino acids from the blood following injection was also an almost constant finding, the amount of drop in these constituents being fairly well in keeping with the percentage composition of the blood, and not sufficient to account for more than 70 per cent of the total drop in non-protein nitrogen. Control experiments showed that after twenty hours of fasting a level of non-protein nitrogen, urea and amino acids is reached in the blood. Pituitrin does not cause a disappearance from the blood of non-protein nitrogen, urea or amino acids. Neither does an extract of serum protein, nor an extract of anterior hypophysis which has been inactivated by boiling. These control experiments indicated that the disappearance of non-protein nitrogen, urea, and amino acids from the blood following the injections of active extracts is probably due to the effect of the growth principle of these extracts. The question arises as to whether or not this disappearance of non-protein nitrogen constituents of the blood may be attributed to increased excretion. It is impossible to draw any final conclusions upon this point, for the amounts of non-protein nitrogen and urea which disappear from the blood are too small to be traced in the urine. Experiments, however, in which the dog is deprived of water, thus cutting down on urine formation, still show appreciable drops in the non-protein nitrogen constituents of the blood after injection, and seem to furnish some evidence against increased excretion as the only explanation of the phenomena observed. Also the fact that the amino acids and the "undetermined nitrogen" portion of the blood decrease after injection seems to indicate that the effect is at least in part of an endogenous nature. The distribution between corpuscles and plasma of the non-protein nitrogen constituents of the blood is apparently not affected by the injection of active extracts of the anterior hypophysis of the ox. The disappearance from the blood of these constituents after injection is in general rather evenly distributed between corpuscles and plasma. Total analysis of the blood of two dogs who had been made definitely acromegalic by daily injections of active extracts of anterior lobe, did not reveal any definite changes in the composition of their blood from what it had been during the control period before any injections had been given. The results of the experiments carried out in the course of this investigation seem to supply some evidence that the growth promoting principle of the anterior hypophysis has an immediate effect upon the non-protein nitrogen constituents of the blood. It seems reasonable that this effect might be, at least in part, one of mobilization from the blood for the building up of new protoplasm.—Authors' Summary.

**The cerebral circulation. XI. The action of the extract of the posterior lobe of the pituitary gland.** Wolff, H. G., *Arch. Neurol. & Psychiat.* 22: 691. 1929.

Extract of the posterior lobe of the pituitary gland causes constriction of pial arteries, arterioles, veins, venules and minute vessels. Vasoconstriction after intravenous injections of pituitary indicates that the diameter of the brain vessels is influenced more by the chemical content of the blood than by its hydrostatic pressure.—Author's Summary.

**The effect of liver on the blood sugar level.** Blotner, H. and W. P. Murphy, *J. A. M. A.* 92: 1332. 1929.

A study of the effect of liver feeding on the blood sugar indicates that whereas previously liver has been regarded as an unsuitable article of food for diabetic patients because of its glycogen content, it is now known to have a beneficial effect on the blood sugar of these patients. The liver fractions that are effective in the treatment of pernicious anemia have no effect on the blood sugar, whereas certain liver fractions that are ineffective in the treatment of pernicious anemia have an effect on the blood sugar like that of liver. Four patients with diabetes, taking liver daily or from three to five times a week, have been observed with repeated blood sugar determinations for approximately one year, while in two, who were followed from twenty and thirty days, it was found that the blood sugar has remained at a constantly lower level than pre-



vicious to liver therapy. These observations suggest that liver contains a blood sugar reducing substance active when taken by mouth, non-toxic, and with an effect on the blood sugar concentration similar to that obtained with insulin. It is difficult to estimate the quantity of liver that will replace a known amount of insulin, but we feel that 180 gm. of liver will have an effect on the blood sugar of certain diabetic patients equal to that of from 10 to 15 units of insulin.

—Authors' Summary.

**The compensatory or preventive action of pancreatic grafts on normal and diabetic glycemia** (*Action compensatrice ou préventive de la greffe pancréatique sur la glycémie diabétique ou normale*). Houssay, B. A., J. T. Lewis and V. G. Foglia, *Compt. rend. Soc. de biol.* 100: 140. 1929.

Extra pancreatic material grafted into normal dogs did reduce the blood sugar, but not below normal limits, regardless of the size or number of the grafts.—J. C. D.

**Effects of pancreatic grafts on variations in glycemia produced by glucose injections** (*Action de la greffe pancréatique sur les variations de la glycémie produites par l'injection de glucose*). Houssay, B. A., J. T. Lewis and V. G. Foglia, *Compt. rend. Soc. de biol.* 100: 142. 1929.

The blood sugar curve showing a rise and return to normal produced in unoperated dogs by injection of glucose is likewise seen in depancreatized dogs carrying pancreatic grafts. The innervation is, therefore, not essential to the incretory action of the pancreas.—J. C. D.

**Effects of large doses of insulin on the blood pressure** (*Action des fortes doses d'insuline sur la tension artérielle*). Jung, L. and L. Auger, *Compt. rend. Soc. de biol.* 99: 1989. 1929.

In dogs, large doses of insulin produce a considerable reduction in blood pressure, which, however, appears slowly.—J. C. D.

**Some effects of long continued insulin administration in rats.** Lee, M. O., *Am. J. Physiol.* 90: 427. 1929.

The effects of continued insulin administration were determined on voluntary activity, blood count, growth, heart rate and oestrous cycle in rats. Insulin was injected twice daily in dosages of 0.1, 0.5 and 1.0 units per 100 grams body weight. Voluntary activity was measured by the revolving cage method with 25 rats. Two periods of one month each with insulin were alternated with two periods of one month without. The voluntary activity was slightly increased during the periods of insulin administration. In 20 rats blood examinations, consisting of erythrocyte, leucocyte and differential leucocyte counts, were made. The only deviation in the insulinized rats was a slight increase in eosinophile cells. Growth was slightly accelerated during the first four months of life in a series of 16 insulinized rats as compared with controls. The heart rate in 10 insulinized adult rats averaged 10 per cent lower than the rate in normal animals, when determined 12 or more hours after the last doses of insulin. In normal rats the administration of insulin in doses insufficient to produce convulsions, caused within 2 hours a decrease of 15 to 20 per cent in the heart rate. This decrease was abolished by atropine. These results are interpreted as due to stimulation of the parasympathetic system by insulin, and point towards an antagonistic relation of insulin and adrenalin. The oestrous cycles in insulinized rats were found to be normal, both as to the total duration of the cycles and the duration of the component stages.—Author's Abst.

**The relation of the liver to the action of insulin.** Murlin, J. R., H. B. Pierce and D. E. Gregg, *Am. J. Physiol.* 90: 458. 1929.

This problem has been studied in three ways: 1, in vitro, employing incubation and aseptic technique; 2, perfusion of the liver; and 3, treatment of dogs having pancreatic diabetes. Under the first method attention has been centered on the proportion of true sugar to non-sugar reducing substances with and without the addition of insulin, before incubation, after incubation for

from 2 to 24 hours, and after hydrolysis of the remaining glycogen. It has been found that the addition of some organic acids profoundly affects the distribution of the reducing substances as well as the total amounts recoverable after incubation and hydrolysis. With the second method it has been shown that with proper precautions there is no demonstrable transformation of fat to carbohydrate in the perfused liver. With the third method, it has been found that the absorption of insulin from the alimentary tract of the depancreatized dog is materially enhanced by various liver products; as bile, salt solution suspension of liver pulp and some extracts. We are inclined therefore to the belief that the favorable effects of liver pulp on diabetes reported by Blotner and Murphy are due to insulin already present in fresh liver, its absorption being aided in certain individuals by bile or its precursors and possibly by some extractive substances.—Authors' Abst.

**The placental transmission of insulin from fetus to mother.** Pack, G. T. and D. Barber, *Am. J. Physiol.* 90: 466. 1929.

Insulin is transmitted through the placenta of the goat from fetus to mother, as determined by variations in maternal blood-sugar levels following intrafetal injection of commercial insulin. The experiments were carefully controlled by the previous determinations of glucose tolerance under the same conditions.—Authors' Abst.

**Metabolism of galactose. VIII. Non-diabetic glycosurias.** Rowe, A. W. and Mary McManus, *Am. J. Physiol.* 90: 502. 1929.

In a series of over three thousand cases correlation studies have been made between the tolerance for galactose, blood sugar levels, and the appearance of a spontaneous glycosuria. The relationship of blood sugar levels and glycosuria in diabetes is contrasted with the same observations in large groups presenting several endocrine and non-endocrine disorders. Analysis of these demonstrates the complexity of the mechanism regulating carbohydrate metabolism and the complete independence of many spontaneous glycosurias from blood sugar levels. Pituitary, thyroid, and ovarian cases presenting certain aberrant functions show glycosuria with normal or low sugar levels, while in disease of the adrenals (Addison's) a glycosuria is frequently observed with blood sugar levels even below a low normal. Of the non-endocrine factors various injuries to the central nervous system, hepatic disorders, syphilis, primary anaemia, and the leukaemias all show a fairly frequent incidence of glycosuria, with only exceptionally a blood sugar level above the conventional normal. The anomalous carbohydrate metabolism during pregnancy is also considered, and the existence of a renal glycosuria discussed.—Authors' Abst.

**Studies on sugar regulation by means of the tolerance for insulin (L'étude de la glycorégulation par le test de tolérance à l'insuline).** Sendrail, M., *Compt. rend. Soc. de biol.* 99: 1901. 1929.

The responses of normal individuals to very small doses of insulin are variable, but fall within fairly definite limits. Reactions outside these limits are a clue to pathological conditions.—J. C. D.

**The utilization of carbohydrate by totally depancreatized dogs, receiving no insulin.** Soskin, S. and W. R. Campbell, *Am. J. Physiol.* 90: 524. 1929.

Totally depancreatized dogs, in which the absence of islet tissue was subsequently verified by post-mortem examination, have been maintained without insulin for as long as four weeks. Fed on protein alone, these animals lose weight steadily, but remain bright and active throughout most of the experiment. For one to two weeks after cessation of insulin administration the animals exhibit an R. Q. of 0.700 or less. The D:N ratio, which starts off at high levels, has frequently fallen below 2.00 by the end of the first week. The ketosis, as judged from urinary excretion, reaches its height about the fourth or fifth day, then steadily declines. During the remaining one to three weeks of the experiment, the R. Q. steadily rises to values as high as 0.900. During this time, the CO<sub>2</sub> combining power and CO<sub>2</sub> content of the blood are not appreciably diminished, and may even rise. The D:N ratio continues to fall, fre-

quently to levels less than 1.00. If insulin be now cautiously resumed, the animal may be revived. It gains weight steadily, and subsequent determinations will again start off with "diabetic" R. Q.'s and D:N ratios. The addition of fifty grams of glucose to the regular diet, from time to time during the latter half of an experiment, results in the retention of a progressively increasing amount of the administered glucose. The glucose retention, often as much as 60 per cent, is accompanied by a variable effect on the R. Q., and a definite lowering of the urinary nitrogen and ketone excretion.—Authors' Abst.

**Insulin in the treatment of pernicious anemia** (*L'application de l'insuline dans le traitement de l'anémie pernicieuse*). Varga, V., *Paris méd.* 19: 249. 1929.

Eight cases of pernicious anemia were treated with insulin and liver extract with highly beneficial results. In particularly severe cases with anorexia, where there is difficulty in taking liver, treatment with insulin is particularly indicated.—M. O. L.

**Diabetes mellitus.** Woltman, H. W., and R. M. Wilder, *Arch. Int. Med.* 44: 576. 1929.

Diabetic neuritis is mainly a sensory disturbance without corresponding motor impairment; pain paresthesia and areflexia are its main characteristics. It shows also a marked predilection for the lower extremities. The histologic material from 10 cases studied clinically is described. Two of these cases are instances of diabetic polyneuritis. In these two cases, isolated bundles of nerve fibers were necrotic. The degeneration noted in the spinal cord is relatively unimportant, and it is doubtful whether it could explain the clinical data. The lesions in the spinal cord do not resemble those found in combined degeneration of the cord seen in pernicious anemia. The most significant lesions are those of the nerve trunks. These are associated in nearly all cases with marked thickening of the walls of the intraneural vessels. The degeneration is more marked toward the periphery. There is good reason to believe that neither glycosuria nor acidosis plays a direct part in the production of diabetic neuritis. In the 10 cases studied, syphilis could be diagnosed in only one, and other complicating infections and intoxications, such as those caused by alcohol and certain metals, were not sufficiently in evidence to explain the neuritis. The results of this study lend support to the opinion that the factor of greatest significance in the lesions of the nerves found in diabetes mellitus is atherosclerosis.

—Authors' Summary.

**Parathyroid therapy in schizophrenia.** Bowman, K. M., *J. Nerv. & Ment. Dis.* 70: 353. 1929.

In 3 cases of catatonia parathormone was given in the hope of lessening the rigidity. Light doses of calcium lactate, as well as thyroid substance, were also used in some of the experiments. Neither the blood calcium nor the catatonic symptoms were significantly influenced.—R. G. H.

**Co-relation of calcium metabolism, parathyroid function and chronic pulmonary tuberculosis.** Ellman, P., *Tubercle* 10: 257. 1929. Abst., *J. A. M. A.* 92: 1390.

Ellman states that the calcium content of the blood serum in pulmonary tuberculosis varies only within normal limits; namely, from 9 to 12 mgm. per 100 cc. The supposed diminution of the calcium content of the blood in pulmonary tuberculosis found by some observers has not been confirmed during the course of this work. In cases responding favorably to treatment the calcium content can be raised, but only within normal maximum limits. The object in view, therefore, in treatment with calcium or parathyroid therapy, is to endeavor to raise the blood calcium to its maximum concentration point. The administration of calcium or parathyroid must be continued over a prolonged period if calcium retention is to be promoted. A combination of parathyroid extract with calcium lactate has proved as effective as any. Microscopic examination of the parathyroid glands in cases of pulmonary tuberculosis shows signs of increased functional activity of the glands. Hence, the conclusion is reached that there is a definite relationship between pulmonary tuberculosis on the one hand, and calcium metabolism and parathyroid function on the other.

**The diuretic action of the parathyroid extract.** Hueper, W. C., *Arch. Int. Med.* 44: 374. 1929.

During the course of experiments with dogs receiving injections of parathyroid extract, it was observed that this hormone has a strong vagotonic effect, evidenced by a decrease of the pulse rate, prolongation of the systole, shortening of the diastole, hyperemia of the vessels of the abdominal organs, and intensification of the peristalsis of the stomach and intestine. When the amount of the injected parathyroid extract was adjusted in such a way that the blood calcium level was raised to about 15 mgm. in 100 cc. of blood, a markedly increased excretion of urine was noticed. Dogs killed during this stage, on histologic examination of the kidneys, showed that the blood vessels, especially the glomerular capillaries, were extremely distended with blood. There were no other changes observed in the kidney, especially no tubular degenerations or calcium precipitations.—R. G. H.

**Carbohydrate metabolism in parathyroidectomized dogs.** Reed, C. I., *Am. J. Physiol.* 84: 230. 1929.

The response of normal and parathyroidectomized dogs to the ingestion of 2 grams of dextrose per kgm. of body weight has been investigated. Dextrose tolerance curves show a characteristic response during attacks of tetany, indicating decreased tolerance. Symptoms are abated after dextrose ingestion or injection. Tolerance tests by intravenous injection give identical results, therefore, an intrinsic mechanism is involved. Intravenous injections of concentrated dextrose solutions will protect dogs during the acute stage and prolong life, but will not prevent the appearance of myotonic symptoms. During tolerance tests the following changes in blood constituents occurred: Calcemia was usually slightly decreased in normal, and non-tetanic animals. In tetany, the decrease was slightly greater. Phosphemia was generally decreased in normal and non-tetanic animals. In tetany, there was always a more pronounced decrease. The Ca:P ratio was always increased. When symptoms were completely abated the final value was above one. These results are believed to indicate an involvement, possibly indirectly, of carbohydrate metabolism in tetany. The fasting level of glucemia was not affected by the operation or the occurrence of tetany.—Author's Summary.

**Carbohydrate metabolism in parathyroidectomized dogs.** Reed, C. I., *Am. J. Physiol.* 90: 490. 1929.

After parathyroidectomy, there is no particular disturbance of fasting glucemia, but when such animals are in tetany, ingestion of dextrose induces a curve of tolerance characterized by a progressive increase and delayed recovery during observation periods of two to three hours. Dextrose ingestion or injection tends to alleviate symptoms of tetany, causing a decrease in inorganic phosphorus and a less pronounced decrease in calcium, thus inclining toward an increase in the calcium:phosphorus ratio. Insulin produced, in normal and non-tetanic dogs, an increased calcemia and decreased phosphemia. When dogs were in tetany, insulin produced characteristic curves of hypoglucemia and hypophosphemia, but calcemia responded much less regularly, any increase being followed by a decrease. Symptoms were usually abated following insulin administration.—Author's Abst.

**The excretion of calcium through the intestine in parathyroidectomized animals.** Taylor, N. B. and A. Fine, *Am. J. Physiol.* 90: 539. 1929.

Using an improved technic, it was found that calcium excretion by the intestine was much augmented in dogs by parathyroid extirpation.—R. G. H.

**Effect of the thyroid-parathyroid apparatus on hyperthermia following injections of adrenin and of salt solution** (*Influence de l'appareil thyroparathyroïdien sur l'hyperthermie consécutive à l'injection d'adrénaline ou de solutions salines*). Viale, G. and J. Kurie, *Compt. rend. Soc. de biol.* 99: 2010. 1929.

After thyroparathyroidectomy, dogs show no rise in temperature following adrenin or NaCl. If the parathyroids alone are destroyed, there is the loss of thermal response. This indicates that it is the parathyroids which are the essential organs.—J. C. D.

**The influence of the thyroid and parathyroid glands upon inorganic salt metabolism.** Aub, J. C., W. Bauer and F. Albright, *Am. J. Physiol.* 90: 270. 1929.

Three individuals were studied. 1. A normal man who was given sufficiently large doses of parathyroid extract to raise the blood calcium level to 12.5 mgm. per 100 cc. 2. A myxedematous woman who was given enough thyroid extract to raise her basal metabolic rate to normal. 3. A woman with exophthalmic goiter who was cured by the surgical removal of her thyroid. Calcium, phosphorus, and total base were determined in both urine and feces, and the urine excretion was analyzed for sulphur, chlorine, and titratable acidity. These subjects received daily the same food, which was inadequate only in calcium. Daily injections of 100 units of Collip's parathormone raised the blood calcium level to 12.5 mgm. per 100 cc., lowered the blood phosphorus level, and increased the urinary calcium and phosphorus excretion. Thyroid administration markedly increased calcium excretion in the myxedematous case without affecting the blood calcium level. The exophthalmic goiter patient excreted 300 per cent more calcium than normal. The effects of these internal secretion variations upon other factors of inorganic salt metabolism were surprisingly slight, and the variations that did occur were in large part due to changes in the nitrogen balance. Thus, the changes in fixed base metabolism are largely adjustments derived from the bone salts.—Authors' Abst.

**Thyroid and cerebral activity. II. Vagus, thyroid apparatus and chronaxie of the sigmoid gyrus** (Thyroïde et activité cérébrale. II. Pneumogastrique, appareil thyroïdien et chronaxie du gyrus simoïde). Cardot, H., J. Régner, D. Santenoise and P. Varé, *Rev. franç. d'endocrinol.* 7: 185. 1929.

The authors have studied the relation of the thyroid gland to cerebral irritability by determining the chronaxie of the sygmoid gyrus (Lapicque technic) before and after section of the vagus innervation of the gland. The chronaxie increases, conversely, stimulation of the vagus fibres lowers the chronaxie. The effects as determined in dogs are evident within a few minutes after nerve section or stimulations.—R. G. H.

**The distinction between metabolic and nervous symptoms in thyroid disorder.** Goodwin, G. M., *Am. J. Med. Sci.* 178: 83. 1929.

Six cases reported emphasize the distinction between symptoms resulting from disturbance of the metabolic and of the nervous mechanism of the body. The rôle of the thyroid in the production of metabolic disorder is obvious. The nervous disorder which, for the most part, represents a disturbance of the autonomic nervous system may be either the cause or the result of thyroid disturbance. There is no reason to believe that disorders of the autonomic system may not result from other agencies than faulty thyroid secretion. The recognition of this fact is important because of the frequency with which a clinical picture made up of nervousness, tremor and tachycardia presents itself. A diagnosis of hyperthyroidism, when these symptoms are present without definite increase in metabolism, should be made with a great deal of reluctance. This is especially important as regards the nervous adolescent girl with a goiter who is often diagnosed and sometimes operated upon for Graves' disease, if minor elevation in metabolism is present.—Author's Summary.

**Thyroneural dystrophy.** Kraus, W. M., S. Brock and P. Sloane, *Am. J. Med. Sci.* 178: 548. 1929.

Two cases are described of a condition defined as thyroneural dystrophy. It is a familial and probably congenital disorder of neuromuscular control of central origin, consisting of any or all of the following: chorea, athetosis, static fits, rigidity, ataxia, abnormal reflex changes, postural defects, and signs referable to disturbed function of the vegetative nervous system, associated with a variable degree of mental and thyroid defect. The condition may be so severe as to imitate precisely advanced cases of cerebral diplegia. Nystagmus, squint and stuttering may be present. No specific pathology is known beyond changes in the internal structure of the cells of the nervous system and a deposit of calcium and iron about the blood vessels. It seems probable that there is a

common but unknown cause of both the thyroid and neural dystrophy. It is well known that a normal thyroid gland is necessary for the development of a normal central nervous system; hence, when thyroid gland is administered early in cases of thyronural dystrophy, the disorders due to the thyroid defect during growth may disappear. In this type of case, thyroid-gland administration is apt to be most beneficial. Reference is made to the possibility of a superimposed toxi-infectious neural involvement due to the letting down of the blood-cerebrospinal fluid barrier for colloids, in consequence of the thyroid insufficiency. Such an hypothesis may explain the late appearance of the nervous symptoms and the ineffectiveness of thyroid therapy.—Authors' Summary.

**Influence of blood, blood serum, and milk on the serum calcium and the symptoms in animals after thyroparathyroidectomy** (*Action du sang, du sérum sanguin et du lait sur la symptomatologie et la sérocalcémie des animaux thyroparathyroïdectomisés*). Parhon, C. J. and Hélène Derevici, *Compt. rend. Soc. de biol.* 100: 37. 1929.

In thyroparathyroidectomized dogs, milk injected intraperitoneally had some ameliorating influence and raised the blood calcium, while blood and blood serum was without effect.—J. C. D.

**Thyroid size in the sexes.** Riddle, O., *Am. J. Physiol.* 90: 495. 1929.

Weights were obtained on the thyroids of 1917 healthy ring doves and on 602 healthy common pigeons aged 4-36 months. Within these age limits there is little or no change in body weight, and in many of the 71 races or strains studied there is little or no change in thyroid weight. The large influence of the hereditary factor in thyroid size, and many well-known physiological factors, have here been adequately equalized or controlled; but thyroid weight nevertheless shows itself to be highly variable. Mean values obtained from the union of all (71) comparable races of ring doves indicate an excess weight (per unit body weight) in the females of 4.5 per cent, or of 1.8 per cent. This mean for 19 races of common pigeons is 7.0 per cent. In general, those races which have the smallest thyroids show the smallest percentage sex difference in thyroid size; in races characterized by large thyroids, the female glands exceed those of the males by a notably higher percentage. We interpret these facts as indicating that many individuals of these races have thyroid enlargements similar to those of endemic goiter; and that, as in the human, the females are more often thus affected than are the males. The rather current impression that the thyroids of human females are larger than those of males is probably supported only or mainly by data from races or regions in which thyroid size tends to be high in both sexes—but specially high in the females—because of slight or pronounced tendencies and approximations to endemic goiter; and also because of temporary enlargements of the female thyroid at certain phases of reproduction.  
—Author's Abst.

**Thyroxin and nutrition** (*Thyroxinwirkung und Ernährung*). Schlossman, H., *Am. J. Physiol.* 90: 505. 1929.

The increase in oxygen consumption under influence of thyroxin is largely dependent upon nutrition. In white rats it was found that any form of "one-sided" diet diminished the metabolic reaction to thyroxin.—Author's Abst. (translated).

**The endocrine toxic epilepsy.** Sereisky, M. I., *Collected Papers, Psychiatric Clinic of the First Moscow State University*, 2: 185. 1927. Abst., *Arch. Neurol. & Psychiat.* 22: 610. 1929.

Epilepsy is often associated with disturbances of the glands of internal secretion. The thyroid gland especially has been mentioned often as being involved in the etiology of various convulsive disorders. The most common form of involvement of the thyroid in epilepsy is connected with hypothyroidism. In a fairly large series, a definite diminution in weight of the thyroid gland up to 20 gm. has been observed. Hypothyroidism in connection with epilepsy is rare. Association of epilepsy with exophthalmic goiter or of the latter with epilepsy is infrequent. Epilepsy may appear before the onset of exophthalmic

goiter, and at times hyperthyroidism precedes the onset of convulsions. The third manner in which hyperthyroidism and epilepsy are associated is when both these conditions appear approximately at the same time. It is in this group of cases that the author is especially interested, and he reports four such. In all these cases there was a history of epileptic personalities among the ancestors. Even before the onset of epilepsy the patients were described as having been extremely egocentric and temperamental, having rigid personalities of the type usually described as "epileptoid." The author believes that there is probably some relation between the two, and postulates a hypothesis that the same toxic factor which caused epilepsy also caused the appearance of the exophthalmic goiter.

**Influence of thyroidectomy and parathyroidectomy on the passage of material from blood to cerebro-spinal fluid** (*Effet de la thyroïdectomie et de la parathyroïdectomie sur le fonctionnement de la barrière hémato-encéphalique*). Stern, L., L. G. Belkina, and A. O. Zlatowierow, *Compt. rend. Soc. de biol.* 99: 536. 1928.

In cats and rabbits, removal of the thyroid was followed after 10 days by a change, which permitted colloids but not crystalloids to pass into the fluid, although normally neither will pass from blood to fluid. Heavy doses of fresh thyroid in normal cats gave the reverse effect. Within two days following thyro-parathyroidectomy in cats, both colloids and crystalloids pass from the blood to the cerebro-spinal fluid.—J. C. D.

**Heart-block, auricular flutter, and adenoma of the thyroid.** Strauss, A. E., *M. Clin. N. Amer.* 11: 487. 1927.

This is the report of a case of thyroid adenoma of 5 years' duration in a woman of 39 years. The basal metabolic rate and other clinical features at first indicated thyroid hyposecretion, but later, during thyroid administration, a distinct picture of hyperthyroidism presented itself. From the beginning there were evidence of heart-block. Electrocardiographic studies revealed the presence of marked auricular flutter with continuation of the heart-block; the auricular rate being 340, the ventricular 42. Thyroidectomy resulted in the disappearance of both thyroid toxemia and auricular flutter.—I. B.

**Effective range of iodine dosage in exophthalmic goiter: Preliminary report.** Thompson, W. O., A. G. Brailey and Phebe K. Thompson, *J. A. M. A.* 91: 1719. 1928. *Abst., A. M. A.*

An attempt has been made by the authors to determine the effective range of iodine dosage in exophthalmic goiter. In 12 of 13 patients at rest in bed in a hospital, as great a reduction in basal metabolism was obtained with 1 drop of compound solution of iodine (about 6 mgm. of iodine) daily as with much larger doses. In 8 of 12 patients more recently studied under the same conditions, half a drop of compound solution of iodine (about 3 mgm. of iodine) daily was as effective as were larger doses. Three patients showed no response to any dose, and one showed slightly a lower metabolic level during the administration of 30 drops daily. The minimum dose that will produce a maximum reduction in basal metabolic rate has not yet been definitely determined. It appears in most cases, however, to be between about one-fifth drop of compound solution of iodine (1.3 mgm. of iodine) and about 1 drop (6.3 mgm. of iodine) daily. There are observations which suggest, but do not prove conclusively, that the minimum dose is perhaps a little less when a patient is at rest in bed in a hospital than when the same patient is at home occupied with her daily routine.

**The cerebrospinal fluid in myxedema.** Thompson, W. O., Phebe K. Thompson, Esther Silveus and Mary E. Daily, *Arch. Int. Med.* 44: 368. 1929.

The concentration of protein in cerebrospinal fluid (lumbar) is high in most cases of myxedema and usually drops to within normal limits following the administration of desiccated thyroid. The concentration of protein in cerebral fluid also appears to be high, although less than that in lumbar fluid. Owing to the high concentration of protein in the cerebrospinal fluid, myxedema

may, in rare instances, be confused with tumor of the brain. The ratio of the chloride content of the spinal fluid to that of plasma is often less after the administration of desiccated thyroid. The rate of flow of cerebrospinal fluid is not less, and may be greater after the administration of thyroid.

—Authors' Summary.

**Pharmacological studies on thyroxin** (*Estudios farmacologicos sobre la teroxina*). Velasquez, B. L., Arch. de med., cir. y espec. 30: 97. 1929.

It was found that neither thyroxin nor cholin gave typical thyroid curves with guinea pig uterus, but such curves were secured by a combination of the two. Since the thyroxin must be administered first, it is supposed to be the sensitiser.—B. C.

**Effect of thyroxin on vagus excitability (electric) in the frog's heart** (*Action de la thyroxine sur l'excitabilité électrique de l'innervation parasympathique du coeur de la grenouille*). Waldenström, deJ., Compt. rend. Soc. de biol 99: 1681. 1928.

*Thyroxin solution does not modify the responses of the isolated frog's heart to vagus stimulation.*—J. C. D.

**The blood supply of the thyroid gland with special reference to the vascular system of the cretin goiter.** Wangensteen, O. H., Surg. Gynec. Obst. 48: 613. 1929.

The alteration in the disposition of the smaller blood vessels in goiter is intimately related to and dependent on the changes in the connective tissue stroma in which the vessels run. In adenomatous goiter, where such changes are common, deviations from the normal size and distribution of the interlobular follicular and capillary vessels are frequent. In the goiter of the cretin, where degenerative changes are especially prevalent, transition from the normal arrangement of these smaller vessels is particularly likely to obtain. Degenerative changes in the vessel walls of arteries of all orders are common in adenomatous goiters. The large extraglandular vessels so frequently seen in cretin goiters represent a compensatory attempt to insure a good blood supply to a benign neoplastic process of a hypofunctioning tissue, in which the alterations in the stroma have made a normal nutrition impossible. In areas of cretin goiters where no departure from the normal is present in the quality and quantity of the connective tissue stroma, giant capillaries may be present in the interfollicular network. Less frequently, such dilated capillaries are also observed in non-cretin adenomatous goiters. The vascular system of the goiter of cretins is not peculiar to cretin goiters alone. Its counterpart, though in less degree, is observed in the vessels of ordinary adenomatous goiters. With its biologically inert tissue, the goiter of the cretin is not able to eke out of its abundant blood supply a nutrition sufficient for normal function.—A. T. C.

**On the biology of iodine and iodine combinations.** von Wendt, G., Am. J. Physiol. 90: 554. 1929.

The results of the last survey of goiter in Finland, together with a plan and the preventive measures already taken, were presented to the XIIth International Physiological Congress at Stockholm. Of the two suitable ways, the one of the direct iodine administration was applied only in a small degree. The indirect method, in which animals were fed a weak iodized fodder, seemed more promising for a country in which the use of milk and milk products is very great. Comparative research showed that this weak iodized mixture of mineral salts, having a composition such that the main defects of the mineral combinations of the usual fodder were corrected, had exercised a favorable influence on the quantity of milk as well as on the fat content of the milk. This favorable result has induced a more extensive use, so that the quantity of one million kgm. of iodized nutrient mixture, which is quite considerable for Finland, will probably be exceeded this year. Continuing the research after the Stockholm congress, a very wide increase of goiter among the domestic animals, especially the pigs and horned cattle, was observed. In districts with much human goiter only few of the calves were without goiter. On one of the estates for experi-



menting we found 72 per cent of the calves with goiter before administration of the iodized mineral salt; after a year of application to the milk cows the number decreased to only 2 per cent. Also an immediate application of the iodized mineral salt mixture to calves with goiter had a good result.

—Author's Abst.

**Exophthalmos following operation for the relief of hyperthyroidism.** Zimmerman, L. M., *Am. J. Med. Sci.* 178: 92. 1929.

Eight cases are reported in which thyroidectomy for the relief of hyperthyroidism was followed by the development of exophthalmos. If some exophthalmos was present at the time of operation, it increased materially afterward. In every case the patients were completely relieved of their symptoms of hyperthyroidism, and the basal metabolic rate was brought to normal or below by the surgical removal of the gland. In three of the patients the eye change was limited to one eye; in the remainder, it was bilateral. Conjunctivitis, chemosis and edema of the lids frequently accompanied the exophthalmos. The post-operative exophthalmos developed with a falling basal metabolic rate, was associated in most instances with subnormal metabolism and sometimes with frank myxedema, and was not accompanied by any other symptom of hyperthyroidism. Thyroid medication or the withholding of it seemed to have no effect on the ocular changes. No definite explanation is offered for this apparently paradoxical phenomenon, though pertinent observations are discussed.

—Author's Summary.



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